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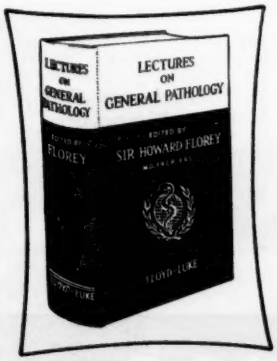

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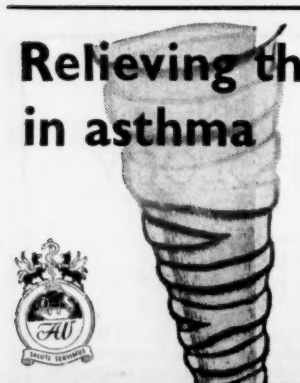

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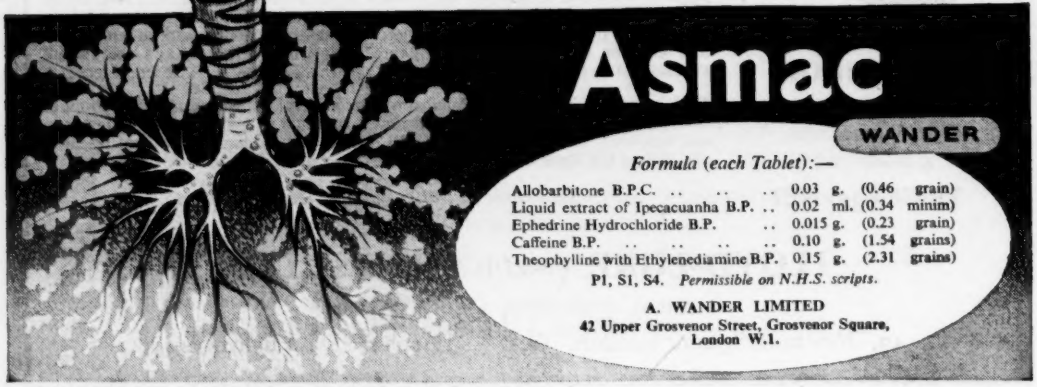

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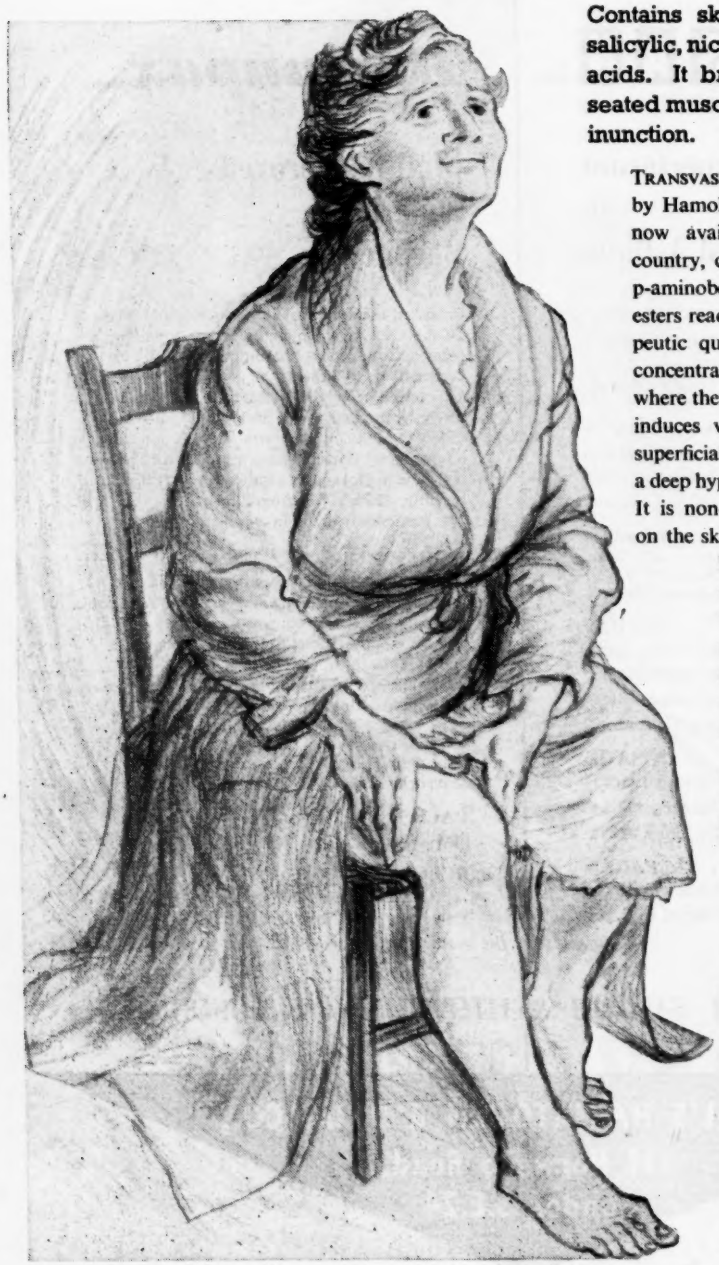

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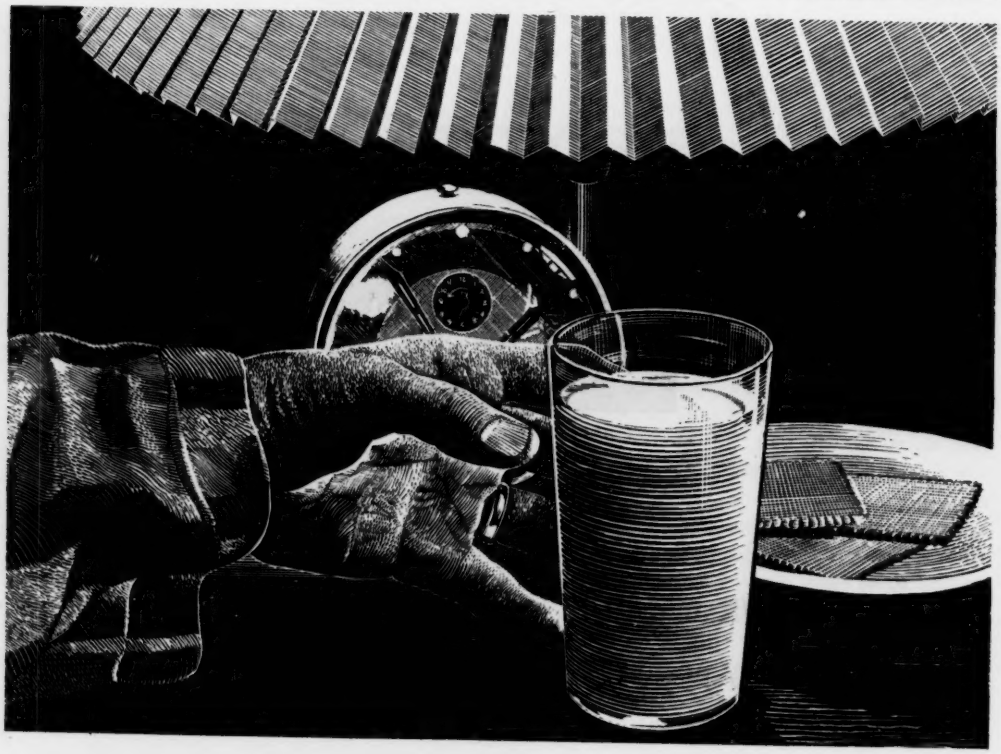

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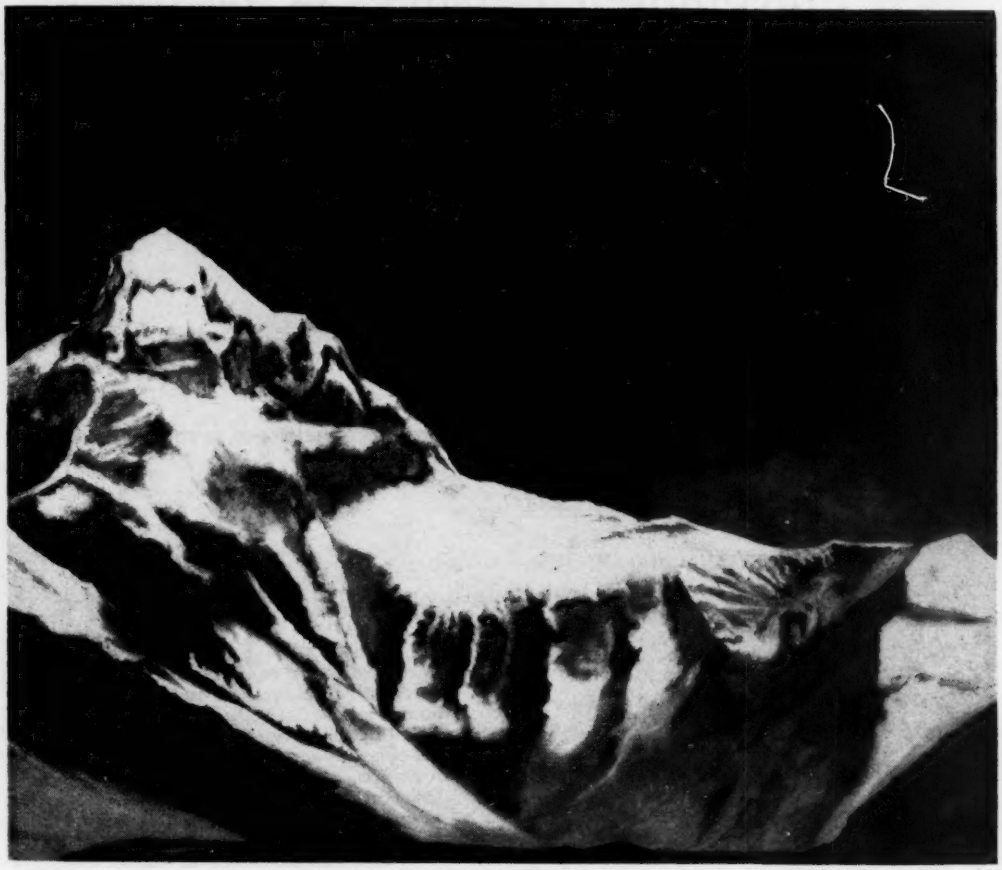

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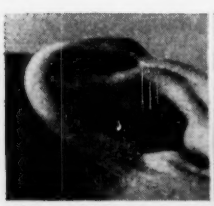

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THE RIDDLE OF THE MAST CELLS

A TRIBUTE TO PAUL EHRLICH *

JAMES F. RILEY
M.D., F.R.C.S.E., D.M.R.T.

From the Department of Radiotherapy, the Royal Infirmary, Dundee, and the Medical School, University of St. Andrews

ON Jan. 17, 1879, the Physiological Society of Berlin heard a remarkable paper by a remarkable young man. The speaker was Paul Ehrlich,[11] a newly qualified doctor; his subject a granular cell of the connective tissues, discovered by him during his student days,[10] for which he proposed the name "mast cell" (*Mast*= food) because he had found them most commonly in those connective tissues whose nutrition appeared to be enhanced. Later he discovered somewhat similar cells in the blood,[12] but he was quick to realise that whereas the comparatively rare blood mast cell (basophil, mast leucocyte) takes origin in the bone-marrow, the more common tissue mast cell is born, lives, and dies in the connective tissues. The similarity of the two types of mast cell lies in their content of cytoplasmic water-soluble granules which stain metachromatically with certain basic dyes.

In view of Ehrlich's later work it is interesting to see in this his first piece of research the beginning of that golden thread which runs through the whole of his working life—the search for "specific affinities" between living protoplasm and known chemicals such as the dyes and drugs that were then appearing. That the biological action of a drug is a direct consequence of its molecular architecture is now a pharmacological axiom so firmly established as to pass without comment. In Ehrlich's day of empirical treatment this concept of chemotherapy was new.

It is said [33] that Ehrlich's curiosity was first aroused in the laboratory in which his cousin Karl Weigert, the histologist, was working. There, chancing to look through a microscope at a prepared slide, Ehrlich fell to speculating on the mechanism which determines the staining characteristics of cytoplasm and nucleus. It must be, he argued, that the chemical configuration of the protoplasm is the opposite of that of the dye; the two fit together like pieces of a jigsaw puzzle or (in the more classical analogy) like a key in a lock. Reasoning thus, Ehrlich conceived that it might be possible to synthesise a dye with affinities specific for the bacterial cell and thereby provide the means of directing a dye or drug selectively to its target in the body.

Fired with this idea, he obtained samples of the latest commercial dyes from the great German chemical dye manufacturers who were then turning to such profitable account Perkin's original discovery in Manchester of the first synthetic dye, mauve. On applying these new dyes to fresh fragments of tissue, Ehrlich observed that the cytoplasm of certain connective-tissue cells contains granules with specific affinities for such basic dyes as dahlia, toluidine-blue, methylene-blue, and neutral red. These granular cells were particularly common around small blood-vessels and evidently formed part of the heterogeneous collection of "embryonal cells" described by his teacher Waldeyer.[52]

Not the least of Ehrlich's attributes was his intuitive understanding of the limitations of the experimental methods of his day. Having discovered and named the mast cells, and having described clearly their morphology, staining properties, and distribution, he left it to others to elucidate the chemical nature of their granules, contenting himself by expressing the hope that some day an interesting function would be found for these mast cells of his.[11] My purpose here is to trace the further story of the mast cell and to see to what extent his hopes have been fulfilled.

The Mast Cell in Evolution

For the sixty years which followed Ehrlich's discovery of the mast cell, research on this subject remained almost entirely histological; and it is of interest to see how far down the evolutionary scale mast cells can be demonstrated.

The volutin granules of protozoa, yeasts, and bacteria have been thought by some to be the homologues of the mast-cell granules in higher organisms.[53] Recent work casts doubt on this view.[49] Nevertheless, in such lowly forms of life as the sponges,[6] starfishes, sea-urchins,[24] and molluscs [25] there are already cells in the mesenchyme with basophilic metachromatic granules in their cytoplasm—by definition mast cells. At the level of the crustaceans mast cells can readily be demonstrated, as Hardy [16] showed, around the arterioles of the crayfish. Many workers have failed to appreciate the high content of mast cells in the tissues of the fish, because here (as in the rabbit) the granules are extremely soluble in water and are lost when the specimen is placed in a watery fixative or stain. In the salmon mast cells are found enmeshed in the collagenous "stratum compactum" in the wall of the gut.[14] They are common in the tissues of the reptiles and amphibia.[27]

Among the warm-blooded vertebrates mast cells occur predominantly in the loose connective tissues and especially around the smaller blood-vessels.[2 10] They are virtually absent from the central nervous system [17] though present in the sheaths of peripheral nerves.[44] In general the parenchymatous organs are poor in mast cells except in the connective tissue of the capsule and trabeculæ.[19 39 51] A noteworthy exception to this is the widespread distribution of mast cells throughout the parenchyma of the dog's liver.[30]

Mast Cells in Pathological Conditions

In choosing the name "mast cell" Ehrlich [11] was influenced by his finding of a high mast-cell content in connective tissues subjected to lymph stasis—especially, as he said, in chronic inflammation and in the environs of tumours.[10 12] In the selective lymphatic blockage of elephantiasis the hypertrophied connective tissue is packed with mast cells,[2] and a similar histological picture on a smaller scale is seen in young well-vascularised keloid.[47]

Tumours composed of mast cells are rare, occurring most commonly in dogs [3 29] and occasionally in cattle.[15] One example has been reported in man.[18] The common mast-cell lesion in man is the skin disease of childhood, urticaria pigmentosa,[50] in which focal collections of mast cells are seen in the dermis. Occasionally urticaria pigmentosa presents as a solitary tumour-like nodule [9 45]; very rarely indeed as a generalised mastocytosis.[13] Finally we may note that an increase of the blood mast cells occurs in chronic myeloid leukæmia, the condition in which Ehrlich [12] first found mast cells in the blood. True basophilic leukæmia is extremely rare.[7]

The Mast Cell and Heparin

In 1937 Michels [27] compiled his monumental review on the mast cells, summarising the literature and citing 25 unresolved hypotheses concerning the function of these cells. Ironically enough in that same year reports came from Scandinavia that the "riddle of the metachromatic granules in the mast cells of Ehrlich" had been solved.[19 22 23]

Swedish workers have been traditionally interested in anticoagulants, and Jorpes [23] and his colleagues in Stockholm had long been working on a powerful anticoagulant first isolated from dog liver and hence called

* Based on a postgraduate lecture delivered in the Medical School, Dundee, on Nov. 19, 1953.

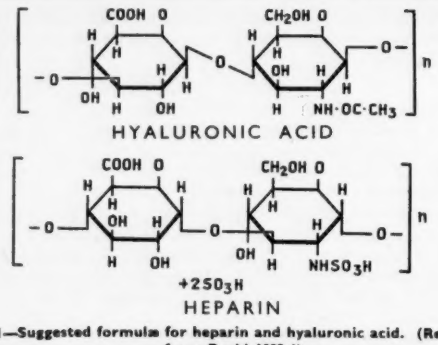

Fig. 1—Suggested formulæ for heparin and hyaluronic acid. (Redrawn from Burkl 1952.[4])

" heparin." Heparin proved to be a mucopolysaccharide rich in sulphate groups, and on finding that heparin stained metachromatically with toluidine-blue Jorpes requested his histological colleagues to search the tissues for metachromatism as a possible clue to the site of formation of heparin.[19] (Cartilage, of course, stains metachromatically, but cartilage has no anticoagulant activity.) It was then that the histologists rediscovered the metachromatic granules in the mast cells and Jorpes was able to show that there is a good correlation between the mast-cell content of a particular tissue and the amount of heparin that can be extracted from it. Point has been given to this work by the recent demonstration of exceptionally high anticoagulant activity in a mast-cell tumour [32]—a small mastocytoma from a dog yielding fifty times as much heparin as the animal's whole liver, the organ from which heparin received its name.

This newly discovered function seemed to provide an obvious and teleologically satisfactory explanation of the perivascular location of the mast cells. Mast cells are perivascular because they produce heparin which they pour into the blood-stream. It was a study of this very relation of mast cells to blood-vessels which led to the discovery of another and completely different function of the tissue mast cell.

The Mast Cell and Histamine

According to Quensel,[34] mast cells occur almost exclusively around capillaries. However, examination of tissues from the rat [36 40] revealed that tissue mast cells commonly arise from undifferentiated precursor cells in the adventitia of somewhat larger vessels with obvious muscle coats. As the cells mature and fill with metachromatic granules they tend to move away from the vessels into the nearby connective tissues and there slowly lose their granule substance. Whatever is released from these granules would appear to be destined for action within the tissues rather than within the blood-stream.

In the search for some function of mast cells other than the production of heparin, it was recalled that a simultaneous release of heparin and histamine could occur from the liver of the dog,[42] and it thus seemed of interest to see if histamine as well as heparin might perhaps come from the tissue mast cells.

The effects of chemical histamine-liberators were first studied,[36 41] and it was found that when a rat is killed quickly by an intravenous dose of fluorescent histamine-liberator the fluorescence is at first sharply localised to the mast cells, especially within the loose tissues of the peritoneum. Thereafter the mast cells break up, and when this has happened the histamine content of the tissue is found to have fallen.[39]

As with heparin,[23] there is also a good correlation between the histamine content of a particular tissue and the number of mast cells which it contains,[37] and this is especially evident when pathological tissues rich in mast cells are examined.[38 39] The lesions of urticaria pigmentosa contain two and a half times as much histamine as the adjacent skin, and with this we may correlate the well-known dermatological observation that light stroking of one of these lesions rapidly produces a reactive weal limited to the lesion itself. The mast-cell content of mouse skin increases on painting with a carcinogenic hydrocarbon, and as this takes place the histamine value also rises. Mast-cell tumours contain exceptionally high quantities of histamine, a pleomorphic mast-cell lesion from a child yielding the unprecedented value of nearly 1000 μg. (1 mg.) histamine per gramme of tissue.

Thus mast cells appear to be as rich in histamine as they are rich in heparin.[42] But when we remember that mast cells are plentiful in lower organisms which lack a blood-vascular system, and that even in higher animals the cells appear regularly to be associated with the tissues rather than with the blood-vessels, we have grounds for doubting whether either heparin or histamine completely answers Ehrlich's riddle. Indeed it seems possible that the production of both heparin and histamine are but part of the mast cell's function, and that there remains unproved a third function which is probably a fundamental interaction between the mast cell and the connective tissues. Such views are admittedly speculative, but at least they may point the way to a further chapter in the story of the mast cells.

Heparin and Hyaluronic Acid

Heparin is a polymer, compounded of disaccharide units consisting of glucuronic acid and an amino-sugar, glucosamine.[23] In this respect heparin closely resembles another naturally occurring polymer of great physiological interest, hyaluronic acid.[4] But whereas the amino-sugar of hyaluronic acid is acetylated, that of heparin is sulphated (fig. 1). It is the sulphate moiety especially which confers on the heparin molecule its anticoagulant

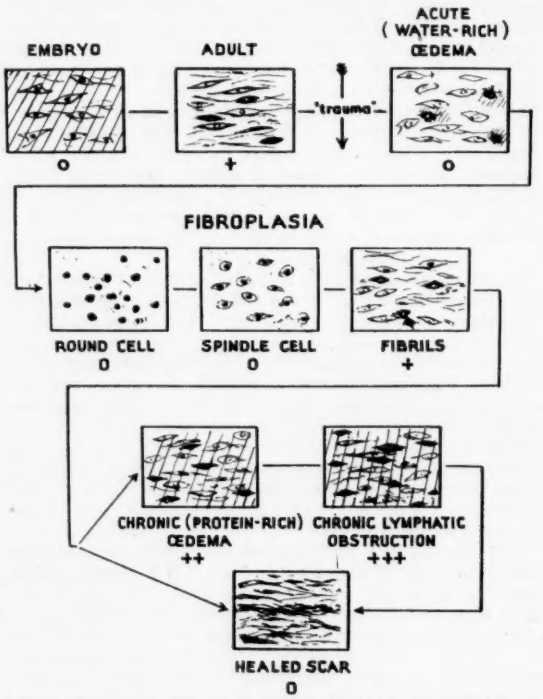

Fig. 2—Diagram to show the participation of the mast cells in the dynamics of the connective tissues. Mast-cell content is indicated by the signs 0 to + + + ; the cross-hatching indicates metachromatic ground substance.

property.[23] On the basis of the similarity of composition of heparin and hyaluronic acid, Asboe-Hansen [1] in Denmark now suggests that the heparin or a heparin-like precursor secreted by the mast cells into the tissues is there gradually desulphated and becomes hyaluronic acid. If the recent formulæ for heparin and hyaluronic acid are correct, so simple a conversion is unlikely; the essential building blocks are there but the internal molecular linkages are different.[4] Nevertheless, the high mast-cell content of loose fibrillary connective tissue generally,[46] and particularly of those specialised clefts in the embryonic mesenchyme which become joints,[1] and the curiously rich mast-cell population of serous membranes and organ capsules [19 39 51] (sites normally coated with a surface film of viscous lubricating fluid), all seem to confirm the view of Staemmler [46] that the mast cells are "unicellular glands of the connective tissue which through their activity produce the mucinous interfibrillary cement."

The participation of the mast cell in the dynamics of the connective tissues is illustrated in the sequence of events shown diagrammatically in fig. 2. Mast cells are

Fig. 3—Mast cells in a fresh spread of ox peritoneum; fixed alcohol, stained toluidine-blue. The cytoplasm is packed with dark metachromatic granules (× 535).

not present in the early embryo, and appear in their characteristic locations only towards the end of embryonic life when they rapidly fill with granules.[26] If, however, the connective tissue is later subjected to trauma—mechanical, chemical, thermal, bacterial—whereby an "acute watery œdema" [8] is produced, the mast cells promptly release their metachromatic substance into the tissues [48] (figs. 3 and 4). The appearance of tissues thus mobilised for regeneration and repair closely resembles the histological condition of embryonic connective tissue.[20] Fibroplasia of shorter or longer duration follows, and, as recognisable collagen begins to take its shape, mast cells once more appear in the reactive zone.[31 46] Should fibroplasia be unduly protracted, as in chronic inflammation, the mast-cell population further increases [11 21]; and in conditions of chronic lymphatic obstruction, in which the tissue spaces remain loaded with protein-rich œdema fluid, both mast-cell hyperplasia and connective tissue hyperplasia become extreme.[2] The end-point of the sequence is reached with the formation of avascular scar tissue in which neither fibroblasts nor mast cells are now present.[21 31]

Such is the observed sequence; the difficulty lies in the interpretation. The cyclic changes in the mast-cell population of loose connective tissue certainly suggest that the mast cells are concerned in some way with

Fig. 4—A part of the same tissue spread as in fig. 3. This area was dipped in water before being fixed with alcohol. There is now disruption of the mast cells; their nuclei stain darkly; and much of the metachromatic material has diffused out of the cells and become attached to adjacent connective tissue fibrils (× 535).

the function of that tissue, and the clue may lie in the distribution of the metachromatic material, despite the reputed chemical differences between heparin and hyaluronic acid. The two types of metachromatism—the diffuse metachromatism of ground substance and the compact granular metachromatism of mast cells—are present alternately in the sequence of changes outlined above, suggesting that whatever their chemical relationship may be they bear an inverse *functional* relation to one another. The metachromatic ground substance present in the embryo would seem to be produced by the connective-tissue cells themselves; but, as cellular differentiation advances and the ground substance shrinks, the metachromatic mucopolysaccharides are seen to concentrate as granules in the tissue mast cells. Indeed, recent work suggests that the granules of mast cells are giant mitochrondria [5 54] some of whose enzymes actively participate in the concentration or synthesis of the metachromatic material whereby mast cells are generally recognised.[35]

* * *

Speculating thus, a hundred years after the birth of Ehrlich, we come back to his original view of the mast cell as a "well fed cell" of the connective tissue. But the riddle is not yet solved and controversy will still surround this problem, as it surrounded so much of Ehrlich's own work. Recalling this latter fact, Sir Robert Muir [28] in writing Ehrlich's obituary notice, remarked "After all, truth needs little defence and nothing can affect the final issue."

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INTESTINAL OBSTRUCTION IN THE NEWBORN

REVIEW OF THIRTY-TWO CONSECUTIVE CASES

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UNTIL comparatively recently, operation for the relief of intestinal obstruction in the newborn held slender hope. But the outlook has been improved by wider recognition of the early symptoms, fuller knowledge of the causes, and earlier resort to surgery.

32 consecutive cases of intestinal obstruction giving rise to symptoms in the first four weeks of life are reviewed here (table I). These babies came under the surgical care of one of us (V. A. J. S.) between January, 1948, and October, 1953, and include only small-bowel and large-bowel obstruction, pyloric and anorectal obstruction having been excluded. Although the series is too small to be of any statistical significance it illustrates the pathology, diagnosis, and management of such cases.

Varieties of Obstruction

DUODENAL OBSTRUCTION: 7 CASES (TABLE II)

Intrinsic Obstruction (4 cases)

In *complete* occlusion of the duodenum due to atresia obstructive symptoms appeared early and persisted. Vomiting, which began as soon as feeding started, was usually copious; abdominal distension was confined to the gastric area and subsided after emptying of the stomach. In most cases straight radiographs showed gas shadows in the duodenum and stomach only (fig. 1)—an appearance which is pathognomonic. The site of obstruction was usually distal to the ampulla of Vater; in one case an atretic portion of the duodenum caused distension of the biliary passages and gall-bladder; at necropsy in another case stenosis was found to be due to a partial septum. At operation, when the duodenum was completely obstructed, gross distension of its proximal portion could be seen; the pylorus was dilated and appeared as a thickened rim, and the transverse colon lay in its normal situation with its mesocolon stretched over the distended duodenum (fig. 2). Enlargement of the duodenum was less when the obstruction was *incomplete*.

In intrinsic duodenal occlusion duodenojejunostomy was carried out in 3 cases and gastrojejunostomy in 1.

Extrinsic Obstruction (3 cases)

The symptoms and signs of this type of obstruction were similar to those of the intrinsic type, and the two types could not be distinguished before operation; radiography was done after a barium meal in case 7 and showed partial obstruction to the flow of barium.

The condition found corresponded to that described by Ladd (1932) in that the duodenum was obstructed by a fibrous band running across the duodenojejunal junction (fig. 3); in addition the colon was malrotated, and the primitive enterocolic loop was free to rotate around the axis of the superior mesenteric vessels. In 2 cases volvulus had taken place, and its correction revealed the maldeveloped arrangement of the gut with the jejunum to the right and the colon to the left of the midline; in one of these cases gangrene of part of the intestine necessitated resection. The importance of dividing the obstructing fibrous bands across the distal duodenum, after untwisting the volvulus, as emphasised by Ladd, was borne out in these cases, all of which recovered.

TABLE I—DISTRIBUTION OF LESIONS IN 32 CASES OF NEONATAL INTESTINAL OBSTRUCTION

Lesion	No. of cases	Died	Recovered
Duodenal:			
Intrinsic:			
Atresia	1	1	0
Stenosis	3	1	2
Extrinsic	3	0	3
Jejunum and ileum:			
Atresia	4	2	2
Stenosis	1	0	1
Meconium peritonitis	2	2	0
Peritoneal adhesions	2	0	2
Meconium ileus	3	2	1
Intussusception	1	0	1
Strangulated hernia	3	0	3
Hirschsprung's disease	9	3	6
Total	32	11	21

ATRESIA AND STENOSIS OF JEJUNUM AND ILEUM: 5 CASES (TABLE III)

Stenosis of the ileum due to a partial septum was present in 1 case and atresia in 4; in the latter the obstructive symptoms and signs presented early and persisted. Radiography of the abdomen showed loops of dilated intestine contrasting with the absence of gas shadows in other parts of the film; the lower the obstruction the more numerous were the distended loops and corresponding fluid levels; these findings were useful in assessing the level of obstruction. In 2 cases of complete obstruction pale waxy trypsin-free stools were passed.

At operation the partial obstruction in case 8 (fig. 4) was relieved by a side-to-side anastomosis above and below the lesion. A year later obstruction recurred at the same site, but after excision of the obstructed segment of bowel and end-to-end anastomosis the infant finally recovered. In all 4 cases of atresia the lesions were multiple: in 1 of these exomphalos was also present, and recovery followed resection of the blind segments of the ileum and repair of the hernia; 2 infants (cases 10 and 11) were re-explored because the primary operation did not relieve the obstruction. In one of these a further site of atresia was found which had been missed by

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TABLE II—DUODENAL OBSTRUCTION

Case no.	Sex	Age at onset	Age at operation	Clinical diagnosis	Anatomical findings	Type of operation	Outcome
1	F	1 day	2 days	Duodenal obstruction	Atresia of duodenum	Gastrojejunostomy	Died
2	F	1 day	9 wk.	Duodenal stenosis	Duodenal stenosis	Duodenojejunostomy	Recovered
3	M	36 hr.	8 wk.	? Pyloric stenosis	Duodenal stenosis	Duodenojejunostomy	Recovered
4	M	2 days	7 days	Duodenal obstruction	Duodenal stenosis	Duodenojejunostomy	Died
5	F	18 hr.	24 hr.	Duodenal obstruction	Extrinsic duodenal obstruction + volvulus + gangrene of jejunum	Correction of volvulus, Ladd's procedure and resection of gangrenous intestine	Recovered
6	M	3 days	7 days	High intestinal obstruction	Extrinsic duodenal obstruction, volvulus, malrotation	Untwisting of volvulus and Ladd's procedure	Recovered
7	F	3 days	4 days	Duodenal stenosis	Extrinsic duodenal obstruction, malrotation	Ladd's procedure	Recovered

omitting to test the patency of the *whole* length of the intestine by distension with saline solution ; in the other (case 11) resection of 10 cm. of terminal ileum which had failed to function after the first operation was followed by clinical recovery, but two months later the baby died from gastro-enteritis. Case 9, with gross jejunal obstruction was a poor operative risk and the child died soon after a limited exploration.

MECONIUM PERITONITIS : 2 CASES (TABLE IV)

This is produced by leakage of meconium into the peritoneal cavity through a hole in the bowel—though the perforation may be closed by the ensuing reaction. In many cases it is associated with a primary obstruction somewhere in the intestinal tract, causing distension of the bowel above (fig. 5) and subsequent perforation (Boikan 1930).

Sterile meconium within the peritoneal cavity seems to act as a chemical irritant, and initiates inflammation which often leads to extensive fibrosis and diffuse calcification.

In case 14 (fig. 5), at operation at the age of 4 weeks, the intestines on the right side of the abdomen were found to be matted and twisted ; after separation of the adhesions, which contained gritty particles, the terminal ileum was short-circuited because it seemed to be obstructed ; the baby died seven hours after operation. At necropsy the abdominal cavity contained much blood, evidently from the surface of the freed bowel ; in the distal ileum an incomplete septum reducing the lumen to 1–2 mm. in diameter was found ; it was surrounded by adhesions, but no hole could be found ; the pancreas was normal.

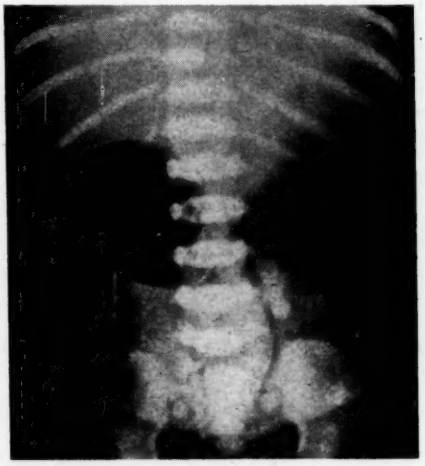

Fig. 1—Duodenal atresia, showing air in stomach and duodenum in contrast to absence of gas shadows from rest of abdomen.

The other case of meconium peritonitis (case 13) has been reported previously (Rashbass 1950). At operation the nature of the obstruction was obscured by dense adhesions in the right side of the abdomen ; it was relieved by ileocolostomy. The infant survived for fifteen months, when necropsy showed duplication of the ileum, cystic fibrosis of the pancreas, and suppurative bronchopneumonia.

PERITONEAL BANDS AND ADHESIONS : 2 CASES (TABLE IV)

In these cases the obstruction giving rise to early symptoms was relieved by operation at the age of 5 and 10 weeks ; in one case adhesions were found in the region of the transverse colon and the liver, while in the other they were more widespread ; both babies recovered after the adventitious bands had been separated. The origin of these bands was obscure, but omphalitis had been present previously in both babies, and one of them had had septicæmia ; possibly the adhesions arose from spread of infection from the umbilicus.

Fig. 2—Duodenal atresia, showing distension of obstructed duodenum, whose retrocolic portion is outlined by interrupted line ; interrupted line in mesocolon indicates site of duodenal opening for duodeno-jejunal anastomosis ; collapsed loops of jejunum are visible in lower part of wound.

MECONIUM ILEUS : 3 CASES (TABLE IV)

Meconium ileus is produced in the newborn by blockage of the bowel, usually the small intestine, by inspissated meconium which becomes dry, tenacious, and sometimes calcified. It is associated with cystic fibrosis of the pancreas. In the present cases the signs and symptoms were those of low intestinal obstruction. In 2 of them abdominal distension was evident at birth : in 1 of these, bead-like masses of hard meconium could be felt on the right side of the abdomen ; in the other a barium enema showed incomplete filling of the descending colon.

At operation in 2 cases much of the distal ileum and colon was found to contain firm pale plugs of inspissated

material, above which the small intestine was grossly distended (fig. 6) with viscid dark-green meconium. The first of these 2 cases was treated by ileocolostomy, and in the second the meconium was removed through an opening in the bowel with the aid of saline lavage, as advised by Hiatt and Wilson (1948). Both infants died, the second baby developing hyperpyrexia and pulmonary hæmorrhages five days after operation. At necropsy cystic fibrosis of the pancreas was confirmed in both cases.

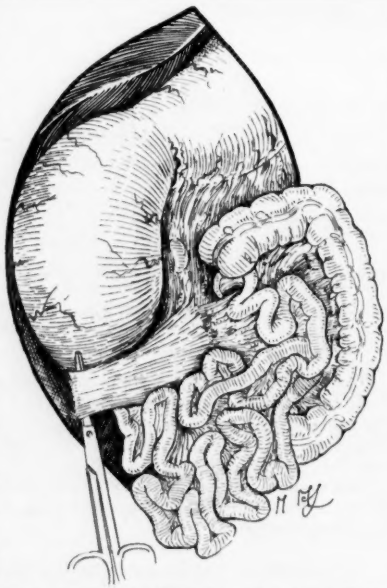

Fig. 3—Extrinsic duodenal obstruction due to fibrous band across duodenojejunal junction; showing mal-developed arrangement of intestines.

The third infant was treated medically with pancreatin, because trypsin was absent from the meconium and the duodenal juice; the symptoms of intestinal obstruction which occurred on the eighth day of life subsided two or three days later without operation.

INTUSSUSCEPTION: 1 CASE (TABLE V)

Obstruction occurred on the eleventh day of life and was accompanied by rectal bleeding. Abdominal colic was not conspicuous, and the intussuscepted bowel could be palpated.

IRREDUCIBLE HERNIA: 3 CASES (TABLE V)

One case presented as a feeding problem, while another had been diagnosed as epididymo-orchitis with gastro-enteritis. All 3 babies recovered.

HIRSCHSPRUNG'S DISEASE: 9 CASES (TABLE VI)

Obstruction is the result of contraction of a variable length of the sigmoid colon. In many cases it is associated with the absence of the ganglionic cells of the intramural plexuses (Bodian et al. 1949). The symptoms came on usually within forty-eight hours of birth; vomiting, often of bile-stained fluid, occurred first and persisted, and was accompanied by increasing generalised abdominal distension and waves of visible peristalsis; there was delay in the passage of meconium, which was usually scanty. On rectal examination narrowing of the pelvic colon was detected in some cases, and sometimes fæcal accumulation could be felt apparently held up by a constriction; the rectum was empty of fæces. Often the passage of a finger or a rectal tube per anum induced a bowel action, with temporary relief of obstructive symptoms. Plain radiography of the abdomen showed distension of both small and large bowel, with fluid levels in most cases. Although the diagnosis of Hirschsprung's disease was suggested radiologically in 2 cases, it was not until later in infancy that the typical segmental narrowing (fig. 7) was clearly demonstrated; with the growth of the child the narrowing portion became relatively longer, and proximal dilatation greater. In later months the distension was intermittent, and from time to time fæcal accumulations could be felt in the large bowel.

Treatment aimed at relieving the intestinal obstruction until such time as the infant was fit enough to stand removal of the narrow segment by rectosigmoidectomy. Simple measures such as laxatives, suppositories, and washouts, which were used in all the cases, were temporarily successful, but in most cases an operation to overcome the obstruction was necessary: in 2 babies, at laparotomy, disimpaction of the fæces through the narrowed segment down into the rectum, followed by the passage of a tube per anum, gave relief; in 3 cases a colostomy was performed because the procedure just described was impossible or had failed to overcome the obstruction. Of the 3 infants who died, a premature baby had, in addition to other congenital anomalies, marked rectal stenosis; another baby died from peritonitis arising apparently from umbilical sepsis; and the third baby, who had string constriction of the pelvic colon, died after a plastic operation at that site.

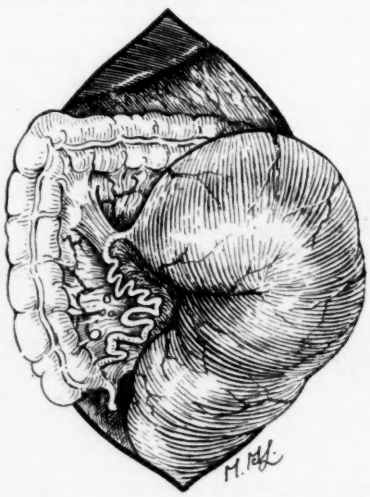

Fig. 4—Intestinal obstruction due to ileal stenosis (case 8).

TABLE III—OBSTRUCTION OF SMALL INTESTINE

Case no.	Sex	Age at onset	Age at operation	Clinical diagnosis	Anatomical findings	Type of operation	Outcome
8	M	At birth	5 days	Intestinal obstruction	Ileal stenosis	Ileo-ileostomy (resection of obstructed ileum a year later)	Recovered
9	F	8 hr.	2 days	High intestinal obstruction	Jejunal atresia	Laparotomy	Died
10	F	At birth	26 hr.	Meconium peritonitis	Multiple ileal atresia and stenoses	Resection (3 operations)	Died
11	F	24 hr.	48 hr.	Low intestinal obstruction	Atresia of ileum	Excision of atretic ileum (2 operations)	Recovered
12	F	At birth	10 hr.	Exomphalos	Multiple atresias + exomphalos	Resection and repair of exomphalos	Recovered

TABLE IV—MECONIUM PERITONITIS, PERITONEAL ADHESIONS, AND MECONIUM ILEUS

Case no.	Sex	Age at onset	Age at operation	Clinical diagnosis	Anatomical findings	Type of operation	Outcome
13	M	At birth	20 hr.	Intestinal obstruction	Meconium peritonitis; ileal stenosis and duplication of ileum (cystic fibrosis of pancreas)	Ileocolostomy	Died at 16 mos.
14	F	At birth	4 wk.	Meconium peritonitis	Meconium peritonitis; ileal stenosis	Ileo-ileostomy after separation of adhesions	Died
15	M	10 days	15 wk.	Intestinal obstruction	Plastic peritonitis	Separation of adhesions	Recovered
16	F	At birth	5 wk.	? Pyloric stenosis	Peritoneal adhesions	Separation of adhesions	Recovered
17	F	At birth	3 days	Colonic stenosis	Meconium ileus (cystic fibrosis of pancreas)	Ileotransverse colostomy	Died
18	F	At birth	20 hr.	Meconium peritonitis	Meconium ileus	Hiatt procedure	Died
19	M	8 days	..	Meconium ileus (cystic fibrosis of pancreas)	..	No operation	Recovered

Discussion

Intestinal obstruction is characterised by vomiting, abdominal distension, and constipation, which vary with the nature, site, and degree of the obstruction.

Vomiting or regurgitation of feeds occurs in the neonatal period in a variety of disorders, such as mismanagement of feeding, stenosis or spasm of the pylorus, hiatus hernia, neonatal infections, and uræmia. Only in a small proportion of cases is vomiting due to intestinal obstruction, and it is important that in these an early diagnosis be made.

Symptoms are usually more troublesome and persistent in complete obstruction, with incomplete obstruction they often vary from day to day.

Fullness of the abdomen at birth suggests intestinal obstruction arising in utero. It may, however, be found in such conditions as fœtal ascites associated with abnormalities of the urogenital tract, dilatation of the bladder due to urethral obstruction, polycystic disease affecting the kidneys or the liver, and abdominal tumours. In meconium peritonitis the abdomen is sometimes distended at birth and in addition the usual signs of obstruction are present: the adhesions may cause intestinal obstruction directly or may exaggerate the symptoms of a pre-existing obstruction. In neglected cases of imperforate anus the abdomen is soft at birth but becomes increasingly distended later. Delay or the infrequent passage of scanty motions, if accompanied by increasing abdominal distension, suggests obstruction. If the meconium is pale and putty-like, there may be a deficiency of pancreatic enzyme in the lower intestine, caused either by complete obstruction or by cystic fibrosis of the pancreas with meconium ileus; in the latter condition the ileocæcal region is filled by a firm pale plug of inspissated material of a waxy consistence closely applied to, but not stuck to, the mucosa; the colon beyond the plug may contain some masses of this material, below which the large intestine is usually empty or contracted; the absence of trypsin from the duodenal juice, when intubation is feasible, and from the meconium will confirm the diagnosis. The obstructive symptoms and signs of meconium ileus are difficult to distinguish from ileal atresia, in which the meconium below the obstruction is of a similar nature and the presence of trypsin in the duodenum is therefore significant. The findings of amniotic squames in the meconium will exclude the presence of complete atresia (Farber 1933).

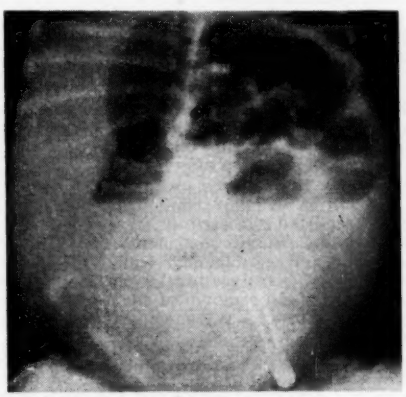

Fig. 5—Radiograph of case 14 showing (1) abdominal distension with obstructed loops of small intestine with fluid levels and (2) areas of calcification on right side.

RADIOLOGICAL EXAMINATION

Plain radiography of the abdomen is invaluable. No special preparation should precede this examination, for previous stomach or bowel washouts may give a false impression of fluid and gas shadows. The pattern of a distended duodenum alone suggests duodenal occlusion (fig. 1), while dilatation of the small or the large bowel indicates the level of obstruction. If the cæcum is seen in its normal position, malrotation of the colon can be excluded; free gas in the peritoneal cavity may result from a perforation of the bowel; intra-abdominal calcification is commonly present in meconium peritonitis, or displacement of the intestine by an encysted mass may be seen (fig. 5). A radio-opaque meal or enema is unnecessary in most cases and should be restricted to doubtful cases when the decision to operate is uncertain. The barium should be emptied through a gastric or a rectal tube after such an examination. In Hirschsprung's disease a barium enema in the first few weeks of life is of doubtful value in the diagnosis.

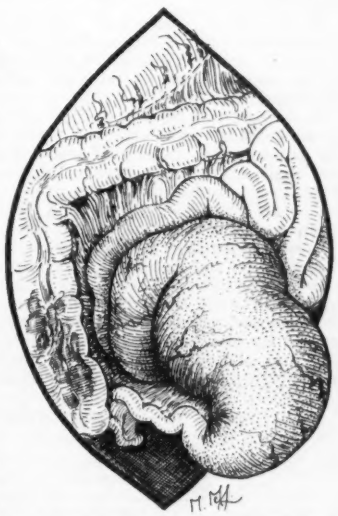

Fig. 6—Obstruction of terminal ileum due to inspissated meconium (case 17).

TABLE V—INTUSSUSCEPTION AND STRANGULATED HERNIA

Case no.	Sex	Age at onset (days)	Age at operation (days)	Clinical diagnosis	Anatomical findings	Type of operation	Outcome
20	M	11	12	Intussusception	Intussusception (ileocolic)	Reduction and ileocolostomy	Recovered
21	M	12	21	Strangulated inguinal hernia	Strangulated inguinal hernia	Reduction and repair	Recovered
22	M	19	31	? Epididymo-orchitis ? hernia	Strangulated inguinal hernia	Reduction after ileo-ileostomy and orchidectomy	Recovered
23	M	21	23	Strangulated hernia	Strangulated hernia	Reduction and repair	Recovered

OPERATIVE CONSIDERATIONS

Treatment is best carried out in a neonatal centre, where suitable nursing and medical facilities are available.

Operation as soon as possible after birth offers the best results. Unfortunately neonatal obstruction often occurs in premature infants, for whom the risk of operation is serious; but it should be borne in mind that unrelieved complete obstruction will inevitably result in death. In cases of incomplete obstruction conservative treatment should not be prolonged if the response is poor or the baby's condition begins to deteriorate.

In most cases correction and maintenance of the fluid and electrolyte loss is necessary, and should be undertaken with mathematical precision (Medical Research Council 1952).

The operative treatment for most conditions causing neonatal obstruction is on well-recognised surgical lines; but there are a few in which the treatment is not so uniform:

In *duodenal obstruction* due to atresia, duodenojejunostomy is the procedure of choice. Extrinsic duodenal occlusion is relieved by division of the peritoneal bands across the duodenum after correcting the associated volvulus.

In *occlusion of the jejunum or ileum* resection followed by anastomosis in continuity is the ideal operation, but the disparity in the size of the bowel above and below the obstruction may present difficulty. Results are better in incomplete obstruction than in complete obstruction. As complete obstruction is often multiple, the patency of the intestine should always be tested.

In *meconium ileus* the results are poor, largely because of the viscid nature of the meconium and the inability of the lower bowel to regain its function after operation. Andersen (1949), in a review of cases of cystic fibrosis of the pancreas, reports that, after she adopted the method devised by Hiatt and Wilson (1948), 5 of her 8 cases of intestinal obstruction due to meconium blockage were successfully treated. Hiatt advocated opening the bowel and removing the sticky meconium by saline irrigation followed by closure of the enterotomy. Gross (1953) recommended Paul-Mikulicz resection of the terminal ileum which contains the firm meconium; Nixon (1953) reported a successful case after a simple enterostomy. To avoid an external ileostomy wound, one-stage resection is preferable; but it may not be feasible, owing to the length of bowel involved or to the degree of obstruction. With all the above procedures pancreatin either locally or by mouth is necessary. Volvulus or meconium peritonitis may complicate meconium ileus; the obstructed loop, being filled with dark-green or brown meconium or fæces, may twist or perforate.

If diagnosed early some cases of meconium ileus respond to conservative measures only (case 19).

After recovery from operation, babies with cystic fibrosis of the pancreas are treated with a high-protein high-vitamin and high-calorie diet, in addition to pancreatin by mouth. Should respiratory infection supervene, chemotherapy will be necessary.

Fig. 7—Barium enema in case 24, showing characteristic appearance of Hirschsprung's disease at age of 10 months.

Meconium peritonitis is usually fatal, but operation holds a hope for recovery. The severity of the peritoneal reaction will depend on the extent of the extravasation of meconium; if this is large it may fill the peritoneal cavity or form an encysted collection limited by the abdominal parietes and adjacent viscera, with the intestine matted round it. If, however, the leak is small, a conglomerate mass of adherent bowel is formed round the perforation; in such cases the coils of intestine will be soiled by meconium-like material and roughened by gritty particles of calcification. When a large collection is present, preliminary paracentesis will decompress the abdomen, and the fluid can be tested for the presence of trypsin; the abdomen is then explored, and any perforation in the bowel closed by fine suturing; in most cases the primary obstruction is difficult to find, but the anatomy may be clarified by gentle separation of the adherent intestines; the obstruction is preferably treated by resection of the affected area.

Until recently the prognosis was poor, but Low et al. (1949), Forshall et al. (1952), and Franklin and Hosford (1952) have reported successfully treated cases.

In *Hirschsprung's disease* treatment consists in relieving the obstruction and establishing regular motions by the aid of enemas and laxatives until such time as the child is old enough to stand removal of the narrowed segment by rectosigmoidectomy. We consider that it is safer to wait until 2 years of age.

In cases in which the obstruction cannot be overcome by simple measures immediate operation is necessary. In such infants, the small bowel and the large bowel are distended, with narrowing usually in the descending or pelvic colon, where an accumulation of firm meconium may be held up; by squeezing this down into the rectum

TABLE VI—HIRSCHSPRUNG'S DISEASE

Case no.	Sex	Age at onset	Age at operation	Clinical diagnosis	Type of operation	Outcome
24	M	2 days	..	? Hirschsprung's disease	No operation	Recovered
25	M	1 day	6 wk.	Low intestinal obstruction	Laparotomy	Recovered
26	M	1 day	5 days	? Congenital rectal stenosis	Colostomy	Died
27	M	1 day	15 days	Stenosis of colon	Laparotomy	Died
28	F	At birth	13 days	Intestinal obstruction	Laparotomy	Recovered
29	F	At birth	5 days	Intestinal obstruction	Colostomy	Died
30	M	3 days	6 mos.	? Hirschsprung's disease	Colostomy	Recovered
31	M	1 day	2 days	? Ileal obstruction	Laparotomy (colostomy at 5 wk.)	Recovered
32	M	2 days	6 mos.	? Hirschsprung's disease	Colostomy	Recovered

and passing a rectal tube the obstruction can be relieved. Where the lower segment is too narrow for this to succeed a colostomy is made.

Even if the newborn child with this condition survives the early obstructive stages, constant supervision is required to guard against a recurrence, laxatives and regular saline washouts being given as necessary. In some cases the inconvenience and risks of frequent bowel washouts and of chronic abdominal distension justify an early colostomy; in others the disadvantages of an abdominal opening are outweighed by the establishment of regular bowel actions and diminished calibre of the colon.

Whether the late results of rectosigmoidectomy are better after the early or the delayed colostomy is uncertain. In each case the progress of the child, the certainty of the diagnosis, and the adequacy of maternal or nursing care should be considered before performing a colostomy.

After operation for these various conditions constant attention is necessary to assist the recovery of these infants. They are usually nursed in an oxygen cradle, and gastric suction is maintained. Oral feeding is withheld till flatus or motions are passed, usually within forty-eight hours; then feeding is gradually introduced, and parenteral fluids are reduced and finally stopped. The discriminate use of antibiotics will lessen the chances of postoperative infection.

PROGNOSIS

Evans (1951), Rickham (1952), Jolleys (1952), and others have drawn attention to the high mortality of intestinal obstruction in infants, which is about 75%; they all emphasised the importance of early diagnosis and the application of modern developments in the management.

Prematurity, other congenital abnormalities, and associated birth injury or infection will increase the mortality.

The symptoms vary with the degree of obstruction: complete obstruction leads to persistent symptoms and rapid deterioration in the baby's condition, and therefore operation should be rarely delayed; whereas incomplete obstruction, with its intermittent symptoms, may cause conservative measures to be unduly prolonged.

Recognition of the coexistence of volvulus and extrinsic duodenal adhesions, as emphasised by Ladd (1932), has led to an increased number of survivors. The identification by Andersen (1938) of cystic fibrosis of the pancreas as a clinical entity has led to a measure of success in the treatment of the associated meconium ileus. In cases of meconium peritonitis, which was until recently always fatal, the occasional success justifies early operation. Gastro-enteritis was a feared complication in the newborn, but should now be rare. In Hirschsprung's disease operation may be required in the neonatal period to save life, and an early diagnosis must therefore be made.

In this series of 32 infants, 11 died after operation and 21 recovered, 19 of whom had undergone operation (table I).

It is encouraging that in recent years successfully treated cases are being more frequently reported than in the past. We may hope that advances in pædiatrics and their surgical application will further improve the outlook.

Summary

32 consecutive cases of neonatal obstruction illustrate the pathology, clinical features, and treatment of duodenal obstruction, jejunal and ileal atresia and stenosis, meconium ileus, meconium peritonitis, intussusception, peritoneal bands, and Hirschsprung's disease. 21 of the infants in this series recovered.

The value of early diagnosis, radiological examination, and detailed attention to supportive measures of resuscitation is emphasised.

The elucidation of such clinical entities as fibrocystic disease of the pancreas, meconium ileus, meconium peritonitis, and Hirschsprung's disease has led to rational treatment. The present mortality of obstruction in the first weeks is more than 75%; but this high figure should be reducible.

We are much indebted to our colleagues, especially Dr. H. M. M. Mackay, Dr. R. H. Dobbs, and Dr. W. F. Young, for their kind coöperation; to Dr. C. J. Hodson and Dr. B. C. H. Ward for the radiological work; and to the nurses, the resident medical officers, and the anæsthetists for their valuable help.

Addendum

Since this article was completed, case 12 has died at the age of five months from congenital abnormality of the heart. There have been 3 further cases. 1 was a premature baby who was operated on unsuccessfully for high jejunal atresia when a week old. In the other 2 intermittent obstruction developed at the ages of 2 and 3 weeks, in each case after a generalised infection; 1 recovered after a week with conservative treatment, while the other is responding slowly to similar management after three months. In both cases the cause of the obstruction is uncertain.

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SUBDURAL COLLECTION OF FLUID IN TUBERCULOUS MENINGITIS

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SUBDURAL collections of fluid have been known since the time of Hippocrates, or such was the opinion of Robert Whytt (1768):

"Hippocrates has enumerated in his second book 'De Morbis' the signs of 'water in the brain,' as his words have been rendered by all the translators. But ἐπί τῳ ἐγκεφαλῳ more properly signifies *upon* than *in* or *within* the brain, and that Hippocrates only speaks here of water lodged between the dura mater and brain can scarcely be doubted, since he proposes to evacuate it by making a perforation in the upper part of the cranium, which operation could have been of no use had the water been contained within the brain itself."

However, it is well known that the cortex may be so thin in gross hydrocephalus that it could have been mistaken for a membrane.

Nowadays subdural collections of fluid are well known, and they fall naturally into two groups: those due to intracranial bleeding, and those which occur in the presence of infection. Penfield (1923) described in a young boy a purulent subdural effusion due to a spread of infection from otitis media; Schiller et al. (1948) described a loculated subdural abscess complicating pneumococcal leptomeningitis due to frontal sinusitis; and since then other subdural empyemata spreading directly from infections of the paranasal sinuses and the middle ear have been described.

More recently attention has been drawn to subdural effusion in children with primary meningitis without any evidence of middle-ear or sinus infection. The two patients reported by Spitz et al. (1945) died of purulent meningitis, which in one case was due to a pneumococcus and in the other to *Hæmophilus influenzæ*; subdural collections of fluid were found post mortem. However, this condition, as well as subdural empyema, was known long before this: Monro (1827) gives an excellent account of both, but of especial interest is his account of a boy who had an encephalomeningocele and undoubtedly died of purulent meningitis. At necropsy turbid fluid was found in the ventricles, and there were bilateral subdural effusions containing, on the right, 6 oz. of clear highly proteinous fluid, and on the left a small quantity of similar fluid. Further cases complicating purulent meningitis have been reported by McKay et al. (1950), Smith et al. (1951), Arnold (1951), Everley Jones (1952), and Guthkelch (1953). Everley Jones noted that in the previously reported cases the organism responsible for the meningitis had been *H. influenzæ* in twenty cases, a pneumococcus in twelve, a paracolon bacillus in one, and *Pseudomonas aeruginosa* in one. The organism in three of his cases was a meningococcus, and he makes the point that subdural effusion had never previously been reported in meningococcal meningitis. Duperie and Dubourg (1913) reported a case in an infant of tuberculous meningitis complicated by a subdural hæmatoma; and McKay et al. (1953) have included a case of subdural effusion due to tuberculous meningitis in a table of figures, but do not refer to it in the text. I have not been able to find any other published report of a subdural collection of fluid complicating tuberculous meningitis; therefore the following case is interesting.

Case-report

A woman, aged 43, was admitted to another hospital on Sept. 15, 1952, in a stuporose condition. She could not describe her symptoms, but her husband said that she had been quite well until four months previously, when she developed, in her back, pain which extended from the cervical region to the sacrum. She had no headache and continued to work about the house and pursue her usual activities until the end of August, when she was sufficiently unwell to take to her bed. A week later she developed in her left shoulder a moderately severe aching pain which radiated down the left arm to the fingers. A few days after the onset of this pain, which persisted, occipital headache came on in such severe paroxysms that she held her hands to her head, cried out, and was completely incapacitated until the pain subsided. Three days before admission she became drowsy and confused, vomited occasionally, and developed acute retention of urine.

On examination she was confused and uncoöperative. Her temperature was normal, her blood-pressure was 170/110 mm. Hg, and she showed signs of dehydration. Her bladder was distended to 6 in. above the symphysis pubis. Examination of the central nervous system showed severe neck stiffness and a positive Kernig's sign but no localising signs. Lumbar puncture produced yellow turbid cerebrospinal fluid (C.S.F.) containing 40 leucocytes per c.mm., and 65 mg. of protein, 500 mg. of chloride, and 22 mg. of sugar per 100 ml. There was a partial block on Queckenstedt compression. Examination of the blood showed hæmoglobin 87% and 13,900 leucocytes per c.mm. (polymorphs 91%). Radiographs of the skull were normal, but a film of the chest showed diffuse miliary tuberculosis. At the hospital to which the patient was admitted she was treated with streptomycin 0·5 g. intramuscularly twice daily and 100 mg. intrathecally, and *p*-aminosalicylic acid 20 g. daily. Two days after admission it was found that the spinal subarachnoid pathway was blocked. The patient's state of consciousness had deteriorated, and she responded only to painful stimuli such as firm supra-orbital pressure and pinching of the facial skin, and it was suspected that the deterioration was due to an increase of intracranial pressure. It was therefore decided to cut burr-holes and make ventricular studies. Streptomycin could also be introduced into the ventricles if indicated. She was accordingly sent to this Unit on Sept. 18, 1952.

Operation.—On arrival at the theatre she was barely rousable, her pupils were equal but reacted poorly to light, and she had bilateral rigidity and extensor plantar responses. Under local anæsthesia bilateral frontal burr-holes were made over the coronal suture 2 cm. from the midline. The dura on the right side was tense, and on opening it there was a gush of clear fluid under pressure. About 50 ml. of this fluid was collected for examination. The cortex was separated from the dura by 1 cm., but no definite membrane was recognised. A cannula was passed into the lateral ventricle, and on the introduction of streptomycin 50 mg. more clear yellowish fluid welled up from the subdural space. The dura under the burr-hole on the left side was opened, and a second collection of fluid was released, rather less than on the right. The cortex here was also depressed.

Postoperative Course.—The patient's condition at the end of the operation was very much improved: she was more alert, could answer questions, and said that she had no headache. She maintained this improvement for four days, but her condition then deteriorated: she developed increasing abdominal tympanites and vomiting, and died on Sept. 24, six days after the effusions had been drained.

Necropsy Findings.—Diffuse miliary tuberculosis of the lungs was confirmed, and scattered tubercles were found in the kidneys. The stomach and intestines were atonic and distended. The brain showed flattening of the cortex over the front of the hemispheres, and some reddening of the dura at the site of operation, but no further collection of fluid was found. There were gelatinous adhesions over the base of the brain, but the striking finding was a thick jelly-like exudate covering the spinal cord from the upper cervical segments to the region of the conus medullaris; this was more organised and clearly of longest standing in the cervical region.

The subdural fluid collected at operation had clotted on arrival at the laboratory, and it must therefore have contained much protein. Attempts to culture tubercle bacilli from the clot failed.

The ventricular fluid was slightly turbid, there was no coagulum; it contained 3 lymphocytes and 183 red blood-cells per c.mm., and 28 mg. of protein and 68 mg. of sugar per 100 ml. The chloride content was not estimated. There was no excess globulin, and attempts to culture tubercle bacilli failed.

Discussion

INTERPRETATION

This patient evidently had miliary tuberculosis, and her central nervous system became involved, beginning with spread to the cervical cord—a rare mode of onset, but important to recognise if such cases are to be diagnosed early enough for treatment to be successful. The history of her illness indicated that some weeks elapsed before the onset of severe headache heralded intracranial extension of the spinal infection. This was followed by rapid deterioration in her level of consciousness which was, no doubt, due to the development of the subdural effusions. As often happens, this patient had widespread foci of active infection in places other than the central nervous system, and death might easily have resulted ultimately from one or other of these.

MANAGEMENT OF TUBERCULOUS MENINGITIS

Since the introduction of streptomycin the management of tuberculous meningitis has undergone very critical examination from time to time, and in recent years it has become evident that surgery has an important but limited part to play, not in a desperate attempt to rescue patients with advanced meningeal infection which, because of inflammatory exudate, is already beyond the reach of streptomycin, but in the treatment of the few cases which, after cure or control of the initial infection, develop a tuberculoma, a tuberculous abscess, or a block somewhere in the cerebrospinal subarachnoid pathways, with resulting hydrocephalus.

In the active stage of tuberculosis attempts to prevent or short-circuit the obstructing granulations in the basal and ambient cisterns have proved disappointing, for in most cases the deterioration has been due not to obstruc-

tion but to neuronal damage following thrombosis of vessels surrounded by granulations.

There are, however, very good reasons for making exploratory burr-holes in any case of tuberculous meningitis when the level of consciousness deteriorates fairly suddenly and evidence of an acute rise of pressure is found.

Cairns (1951) described two cases in which the intracranial pressure rose suddenly. One of these patients died and was found at necropsy to have a tuberculous abscess in the left parietal lobe. The other, a boy aged 3 years, developed signs of an acute rise of intracranial pressure and was found to have localised hydrocephalus of the temporal horn of the right lateral ventricle; this was relieved by operation and he recovered.

A third case which illustrates the importance of burr-holes and ventriculography was recently transferred to this Unit from another hospital. This patient, a married woman aged 26, had been treated for about three months for tuberculous meningitis and had made a good recovery, when she began to have severe intermittent headache suggesting attacks of hydrocephalus. Ventriculography revealed a space-occupying lesion in the right cerebellar hemisphere, and at operation a tuberculous abscess was successfully removed.

In the present case the subdural collection of fluid rapidly produced a severe impairment of consciousness. This was immediately relieved by drainage; so possibly more cases of subdural effusion await discovery in patients with tuberculous meningitis whose symptoms suggest raised intracranial pressure of acute onset, and drainage may be beneficial and even life-saving.

ÆTIOLOGY OF SUBDURAL COLLECTIONS OF FLUID

The ætiology of subdural hæmatoma and hydroma resulting from trauma is well understood; so it is sufficient here to point out that in both conditions the arachnoid may be torn (Quincke 1906, Hardman 1939). The cause of subdural collections of fluid associated with meningitis is not so clear, but they are probably in most cases also due to rupture of the arachnoid membrane. Although Spitz et al. (1945) have been widely cited as believing that these effusions are due to escape of blood from a thrombosed subdural vein, they suggested five different possible mechanisms.

(1) *Direct Extension through a Necrotic Arachnoid Membrane, either at the Arachnoid Villi or over the Hemispheres.*—This is an obvious mechanism of spread of infection to the subdural space in cases where the causal organism has strong cytolytic power, but this has been a necropsy finding in cases of virulent infection (especially by *H. influenzæ*) and is unlikely to explain the effusions found in mild cases.

(2) *Simple Transudate through Damaged Arachnoid.*—This theory has received support from Smith et al. (1951), Everley Jones (1952), Gitlin (1952), Guthkelch (1953) (for effusions containing little protein), and McKay et al. (1953). It is natural to believe that a membrane such as the arachnoid could permit transudation when it is inflamed, just as do the pleura and peritoneum. It is, however, very unlikely that simple transudation can be the sole cause, because all cases of meningitis are accompanied by meningeal inflammation, yet few of them develop subdural effusions of sufficient size to cause symptoms.

(3) *Escape of Blood from Thrombosed Vein.*—Aseptic thrombosis of cerebral veins and sinuses is known to be associated with intracerebral, subarachnoid, and subdural hæmorrhage (Russell 1949, Barnett and Hyland 1953); but in such cases the bleeding has clearly taken place not from thrombosed subdural veins but from engorged capillaries in areas of infarction. Guthkelch (1953) suggested that this might be the mechanism in effusions containing much protein; but the protein content of effusions, like that of C.S.F., varies with the infecting organism and the chronicity of the disease.

(4) *Involvement of Subdural Space secondary to Thrombosis of Venous Sinus.*—It is most unlikely that this is the cause of subdural collections, since the incidence of such effusions has not lessened with the advent and use of antibiotics, which are very effective in preventing sinus thrombosis; and the fact that sinus thrombosis and effusions may be present together is not proof that the one is the cause of the other.

(5) *Simultaneous Involvement of both Arachnoid and Dura by Blood-borne Infection.*—Although Spitz et al. (1945) had no evidence from their material that this ever happened, they mention this theory, which may be very important. Consideration of the portals of entry of meningitis leaves little doubt that focal embolic sepsis in the bone, the emissary veins, or the cortex may be the start of meningitis, brain abscess, and subdural infection (Johnson 1953).

Rupture of Arachnoid Membrane.—I suggest an alternative mechanism—simple rupture of the arachnoid membrane due to raised subarachnoid pressure.

In meningitis, probably because of arachnoidal inflammation and impaired absorption of C.S.F., the subarachnoid pressure is raised. An inflammatory exudate from the vascular pia-arachnoid passes into the subarachnoid space and, together with œdema in the underlying cortex, produces obstructions at various places in the cerebrospinal subarachnoid pathways.

The arachnoid mater is normally thinner over the hemispheres than at the base and, unlike the pia mater, bridges over the sulci, except where it dips into them a little on the walls of emerging veins. The subarachnoid space is shallow over the summits of the gyri but deeper over the sulci, and the pia and arachnoid are connected by fine connective-tissue trabeculæ. These trabeculæ are not normally under tension.

With exudate adding to the volume of fluid in the ventricles and subarachnoid space, and at the same time seriously diminishing absorption at the villi, the intracranial tension rises, the brain becomes œdematous, and the gyri become wider, partially obliterating the sulci and squeezing the fluid out of them. This fluid, which may be loculated by adhesive arachnoiditis, distends the subarachnoid space and tears the delicate arachnoid, allowing a spurt of C.S.F. and exudate to reach the subdural space. Tight trabeculæ may determine the point of rupture.

Once in the subdural space, such a collection would tend to spread, and the protein in it might form a membrane which would become vascularised by new capillaries from the dura. Moreover, once the effusion had formed, the obstruction to the absorptive area would be increased and a pressure gradient would exist from the subarachnoid space, deep to the thin inner membrane of the effusion, to the arachnoid villi adjacent to the sinus. This would probably increase the effusion, aided perhaps by osmosis and a leakage of red cells from the membrane as its young vessels were stretched.

That effusions are a result of a tear in the arachnoid is supported by Cairns et al. (1946), who described a trial of intrathecal penicillin in a case of suppurative meningitis. Penicillin was administered by lumbar puncture, and twelve hours later it had disappeared from the C.S.F.; so these workers introduced penicillin directly into the ventricles. On making frontal burr-holes they found a large subdural collection of yellow fluid containing 0·5 units of penicillin per ml., while the ventricular fluid contained 1 unit per ml. Some of this penicillin must clearly have passed through a hole in the arachnoid membrane. It did not simply diffuse, for after the injection of 8000 units of penicillin into the subdural space at the site of the effusion none appeared in the C.S.F., indicating that either the hole had closed or it was a valve-like one-way opening.

Everley Jones (1952), by injecting indigo carmine into an effusion, showed that effusions do not remain in contact with the subarachnoid space. Further evidence that rupture of the arachnoid may follow increased subarachnoid pressure is to be found in descriptions by Dandy (1944), Bassett and Lemmen (1952), and Logue (1951) of subdural hæmatoma complicating subarachnoid hæmorrhage.

The rarity of subdural collections in tuberculous meningitis may possibly be explained by the fact that

sudden rises in subarachnoid pressure with distension of the subarachnoid space are rare in this disease.

Summary

A fatal case of subdural collection of fluid complicating tuberculous meningitis is described.

It is important to make burr-holes in cases where the level of consciousness suddenly deteriorates.

A tear in the arachnoid is probably the important factor in the ætiology of subdural collections of fluid.

I wish to thank Dr. G. H. H. Benham, who referred the case, for the use of his records and the necropsy report; Sir Geoffrey Jefferson, F.R.S., for drawing my attention to Monro's book; and Mr. R. T. Johnson, O.B.E., F.R.C.S., for permission to publish and for kindly advice and criticism.

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POST-TRANSFUSION SURVIVAL OF RED CELLS STORED AT −20°C

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RED blood-cells mixed with glycerol can be frozen to −79°C and thawed without hæmolysis (Smith 1950). If the cells are freed from glycerol and transfused they survive normally in the recipient's circulation (Sloviter 1951, Mollison and Sloviter 1951). Red cells suspended in citrate-plasma and mixed with an equal volume of 30% (*w/v*) glycerol in 0·9% saline solution (i.e., final glycerol concentration 15% *w/v*) undergo progressive lysis if stored at −79°C, with the result that after six months only 60% of them may be recovered. However, these red cells have an almost unimpaired survival in vivo (Mollison et al. 1952). Red cells stored in the same mixture at −20°C undergo even more rapid lysis; but the cells recovered after three months' storage may survive well in vivo (Mollison et al. 1952). This last finding suggested that at −20°C chemical changes in red cells might be virtually arrested and that, if physical damage could be prevented, prolonged storage at −20°C could be achieved. −20°C is a temperature that can be maintained very easily—for example, in an ordinary ice-cream cabinet. It would therefore be a great advantage if prolonged preservation of red cells were possible at this temperature rather than at some lower temperature.

Chaplin and Mollison (1953) reported that, if red cells were mixed with citrate-glycerol rather than with saline-glycerol, and if the final concentration of glycerol were raised from 15% (*w/v*) to 30% (*w/v*), the rate of hæmolysis during storage at −20°C was enormously reduced. After three months' storage 98% of the red cells were intact. In view of the previous demonstration that red cells stored at −20°C for three months survived normally, it seemed likely that red cells stored in the new solution would survive well; but these workers pointed out that measurements of survival in vivo would have to be made before the usefulness of the method of storage for transfusion was established.

We report here mainly the post-transfusion survival of red cells stored in different glycerol mixtures at −20°C. Red cells stored in the citrate-glycerol mixture originally described do not survive well, but in slightly modified mixtures survival remains very good until the period of storage exceeds three months. Thereafter viability is lost progressively with time. Red cells stored at −20°C slowly consume dextrose, and their loss of viability is probably due to the fact that chemical changes are not completely arrested at −20°C.

Methods

STORAGE TEMPERATURES

A temperature of about −20°C was maintained in a 'Prestcold' refrigerator cabinet, model CC 82. Bottles of blood for transfusion were kept in the lower compartment, in which the temperature ranged from −21°C to −24°C. Smaller samples of blood were kept in the upper compartment of the refrigerator, in which the temperature ranged from −18°C to −20°C. For convenience storage in the range from −18°C to −24°C is referred to here as "−20°C."

A few experiments made at other temperatures are included here. These temperatures were maintained as follows:

For storage at −79°C a special insulated box was used containing a large tank in which solid carbon dioxide was placed as often as necessary, and a smaller tank containing alcohol in which the bottles or tubes of blood were kept. Solid carbon dioxide was added to the alcohol bath two or three times a week; this kept the temperature in the bath between −75°C and −79°C. Occasionally the temperature in the bath rose to −70°C. A temperature of −10°C was maintained in a cold-room, and +4°C in an ordinary domestic refrigerator.

BLOOD-GLYCEROL MIXTURES

Red cells of group O type M or of group A type N were obtained from blood collected at routine bleeding sessions of the North London Transfusion Centre. This blood was taken into A.C.D. solution (disodium citrate 2 g., dextrose 3 g., water 120 ml., mixed with 420 ml. of blood) and stored for either twenty-four or forty-eight hours at +4°C. The red cells were next packed by centrifugation, and almost all the supernatant plasma-citrate solution was removed. The bottles usually contained about 230 ml. of packed red-cell suspension; it was estimated that about 20 ml. of this volume consisted of plasma citrate either trapped among the red cells or lying on the surface of the suspension. To this packed-cell suspension was added an equal volume (about 230 ml.) of one of the following mixtures:

Solution I (trisodium citrate/glycerol).—This mixture was the one described by Chaplin and Mollison (1953). 40 volumes of glycerol was added to 60 volumes of 5% trisodium citrate (the pH of this solution is 7·7). On the assumption that glycerol diffuses freely into 60% of the red-cell volume, the final concentration of glycerol after mixture with the packed cells is 30% (*w/v*), or 3·3 *M*; citrate is assumed not to penetrate the red cells, and its final concentration in this

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mixture is therefore 0·1 *M*. In two additional experiments described below this solution was modified to give a final glycerol concentration of 20% and 40%.

Solution II (*tripotassium citrate/glycerol*).—40 volumes of glycerol was added to 60 volumes of 5·5% tripotassium citrate (final concentration of citrate about 0·1 *M*).

Solution III (*buffered tripotassium citrate/glycerol*).—40 volumes of glycerol was added to 60 volumes of a solution containing tripotassium citrate 3·25%, dipotassium hydrogen phosphate 0·6%, and potassium dihydrogen phosphate 0·47% to give the following final concentrations: citrate 0·06 *M*, each phosphate 0·02 *M*. The pH of this solution is 6·9.

Solution IV (*plasma citrate/glycerol*).—150 ml. of supernatant plasma-citrate was saved after centrifuging the blood and mixed with 90 ml. of glycerol and 9 ml. of 30% trisodium citrate (solution IVa) or with 20 ml. of 30% citrate (solution IVb). The concentration of citrate is about 0·05 *M* (IVa or 0·09 *M* (IVb), and the pH of the solution is 7·4. The final concentration of glycerol after mixture with red cells is 3·3 *M*.

A few investigations were made with two other solutions: (1) in one solution "dextran-citrate-glycerol," dextran (Bengers) was substituted for plasma-citrate in mixture IVa (the final concentration in this mixture was 0·03 *M*); and (2) in the other solution "lactate-glycerol (with added calcium)," 1 volume of the following solution was added to 1 volume of packed red cells from heparinised blood: glycerol 40 volumes mixed with 60 volumes of sodium-lactate solution to give a final concentration of 0·16 *M*; calcium chloride was added to give a final concentration of 0·005 *M*.

In each case the glycerol solution was added slowly to the packed red cells with constant agitation of the mixture. After about thirty minutes the bottles were placed in the —20°C refrigerator.

In some further experiments blood was kept solely for tests in vitro; in these cases heparinised blood was used. Packed red cells were obtained by centrifugation and mixed with one of the four solutions already described or with various modifications described below in the results.

REMOVAL OF GLYCEROL FROM RED CELLS AFTER STORAGE

The blood was thawed by placing the container in water at 40°C and agitating it until no ice was visible. The mixture was then centrifuged and the supernatant fluid replaced by a solution containing 16% glycerol in 3% trisodium citrate. The solution and red cells were well mixed and then immediately centrifuged again. The supernatant fluid was now replaced with 8% glycerol in 3% citrate and then successively with 4% glycerol in 3% citrate, 2% glycerol in 3% citrate, and saline solution. Either two or three washes in saline solution were used. The red cells were finally suspended in an approximately equal volume of saline solution.

In a few cases the glycerol content of the final supernatant solution was estimated by oxidation with periodic acid and determination of the formaldehyde formed (Karnovsky and Brumm 1954, MacFadyen 1945).

ESTIMATION OF HÆMOLYSIS IN VITRO

The percentage hæmolysis in a sample was calculated as follows:

The hæmoglobin concentration sample of the supernatant fluid (Hb_s) and of the whole (Hb_w) were determined in a photo-electric colorimeter with an Ilford 625 filter. Percentage hæmolysis was expressed as

$$\frac{Hb_s \times \frac{100 - \text{P.C.V.}}{100}}{Hb_w} \times 100,$$

P.C.V. being the packed-cell volume of the whole sample.

In most cases appreciable additional hæmolysis occurred during the washing of the red cells to remove glycerol. The over-all recovery of red cells was estimated as the total hæmoglobin content of the sample after washing, divided by the total hæmoglobin content of the sample immediately after thawing.

MEASUREMENT OF SURVIVAL IN VIVO

All the recipients were of group A type M, and most of them were women whose anæmia was related to pregnancy or to parturition. To ensure an adequate rise in hæmoglobin concentration, fresh blood of group AM was often transfused in addition to the stored red cells (of group OM and AN).

Transfused red cells in the recipient's blood were counted after differential agglutination by Dacie and Mollison's (1943) modification of Ashby's method. Counts were made twenty-four and forty-eight hours after transfusion and after a week; in most cases further counts were made at intervals until most of the transfused cells had been eliminated.

The sera used were either anti-M powdered globulin obtained from Lederle Laboratories or anti-A produced in rabbits by the method of Morgan (1943); with the anti-M serum pre-transfusion ("blank") counts were 5000 or less per c.mm. in each of 19 cases, and with the anti-A serum 10,000 or less per c.mm. in 15 out of 19 cases; in the remaining 4 cases the blanks were between 12,000 and 25,000 per c.mm.

The concentration of transfused cells expected on the day after transfusion, if 100% had survived, was calculated from the formula:

$$\frac{\text{number of red cells transfused}}{\text{total red-cell volume}} \times \text{P.C.V.}$$

(No allowance was made for the small fraction of red cells—about 0·85%—which would be expected to disappear in a day.)

The number of red cells transfused was estimated from the volume and red-cell count of the transfused red-cell suspension; the volume was calculated by weighing the bottle with its contents before and after transfusion and determining the specific gravity of the cell suspension; the red-cell count of a well-mixed sample was determined by counting not less than 4000 red cells.

Red-cell volume was determined, on the day after transfusion, by a modification (Chaplin 1954) of the ^{32}P method of Reeve and Veall (1949).

Packed-cell volume was determined in Wintrobe hæmatocrit tubes spun for fifty-five minutes at 3000 r.p.m. in a centrifuge of radius 15 cm.; correction for trapped plasma was made by the method of Chaplin and Mollison (1952).

The packed-cell volume of a sample taken forty-eight hours after transfusion was often a little higher than that of a sample taken at twenty-four hours. Accordingly, in estimating the percentage survival at forty-eight hours and subsequently, the predicted 100% survival, calculated as described above, was corrected by the factor:

$$\frac{\text{P.C.V. two days after transfusion}}{\text{P.C.V. one day after transfusion.}}$$

No corrections were made for changes in P.C.V. after forty-eight hours since many of the recipients were anæmic women in whom the rise in P.C.V. during the period of the observations was due partly to an increase in red-cell volume.

CHANGES IN CELL VOLUME

Mean cell volume (M.C.V.) was determined in the usual way from packed-cell volume and red-cell count (4000 cells counted); it was arbitrarily assumed that initially M.C.V. was 90 c.μ in all cases, and observed values were expressed as percentages of this figure. A second estimate of cell swelling or shrinking was obtained by measuring mean corpuscular hæmoglobin concentration (M.C.H.C.) from the hæmoglobin concentration and packed-cell volume of the sample; it was assumed that the M.C.H.C. was initially 34%, and departure of observed values from this figure was taken to indicate alteration in cell volume. In 50 cases in which changes in cell volume were estimated

TABLE I—POST-TRANSFUSION SURVIVAL OF RED CELLS STORED ABOUT TWELVE WEEKS IN VARIOUS SOLUTIONS AT —20°C

Solution	No. of cases	Average period of storage (weeks)	Percentage survival after transfusion (days)		
			1	2	7
I. Trisodium citrate/glycerol ..	7	12·6	56	48	44
II. Tripotassium citrate/glycerol ..	5	12·6	64	64	59
III. Buffered tripotassium citrate/glycerol	3	13·3	84	80	73
IV. A.C.D. plasma-citrate-glycerol ..	6	12·2	92	89	84

by these two methods the standard error of the difference between the two estimates, expressed as a coefficient of variation, was 8%.

In table II the figure given for cell volume (expressed as percentage of normal) is the mean of estimates obtained by the two methods.

INTRACELLULAR SODIUM AND POTASSIUM CONCENTRATIONS

Sodium and potassium concentrations were determined with the flame photometer (Domingo and Klyne 1949) by the method of Selwyn and Dacie (1954). The results were corrected by the factor

$$\frac{\text{M.C.V. after storage}}{\text{M.C.V. before storage}}$$

to allow for changes in cell volume; M.C.V. before storage was assumed to be 90 c.μ.

OSMOTIC FRAGILITY

The method of Parpart et al. (1947), as modified by Crawford et al. (1953), was used.

ESTIMATION OF DEXTROSE

Experiments were made to compare the rate of dextrose consumption by red cells at different temperatures. Dextrose was estimated by the method described by King (1951), except that the blood was pipetted into distilled water instead of isotonic sodium-sulphate solution; and thus the estimate of dextrose concentration includes some of the reducing substances in red cells. In preliminary tests it was shown that the presence of glycerol did not interfere with the estimations.

TABLE II—INTRACELLULAR CATION CONCENTRATION, CELL VOLUME, AND OSMOTIC FRAGILITY IN RED CELLS STORED FOR ABOUT THREE MONTHS AT —20°C IN FIVE CITRATE-GLYCEROL MIXTURES

Solution	No. of samples	Period of storage (weeks)	Mean survival in vivo at 24 hours (%)	Intracellular cation concentration (m.eq. per litre)			Cell volume (% of normal)	Median osmotic fragility (% NaCl)
				Na	K	Total		
I. Trisodium citrate/glycerol ..	3	11–13	63	49	16	65	76	0·264
II. Tripotassium citrate/glycerol	3	10–15	64	14	45	59	74	0·276
III. Buffered tripotassium citrate/glycerol.. ..	2	14–15	84	19	68	87	88	0·350
IVa. A.C.D. plasma-citrate-glycerol	2	11–12	92	65	31	96	86	..
IVb. A.C.D. plasma-citrate-glycerol	1	14	78	65	20	85	88	0·350
Normal values ..	..	..	..	15	100	115	100	0·424

The intracellular cation concentrations have been corrected for changes in cell volume. The median osmotic fragility is in some cases derived from single samples only.

Red cells from heparinised blood were mixed with trisodium-citrate glycerol (solution I), and then sufficient dextrose was added to bring the final concentration to 90–140 mg. per 100 ml. Aliquots of the blood were then stored at each of the following temperatures: —79°C, —20°C, —10°C, and +4°C. At intervals a sample stored at each of these temperatures was thawed and its dextrose concentration estimated.

RED-CELL ANTIGENS

Blood from 7 donors was stored at —20°C in citrate-glycerol mixtures for a year. In most cases the blood mixtures were stored in 2–3 ml. amounts in small tubes. The ability of the red-cell antigens to react with standard antisera was tested at intervals during the year. After three months' storage samples were tested with only a few antisera (anti-A, anti-M, anti-N, anti-S, anti-P, and anti-D); after five months' and twelve months' storage at least two samples were tested with anti-A, anti-M, anti-N, anti-S, anti-D, anti-C, anti-c, anti-P, anti-Le^a, anti-Le^b, anti-Lu, and anti-Fy^a; only one sample was tested with anti-B, anti-E, and anti-K.

On the day of the test a fresh sample of blood was taken from the same donor, and 1% cell suspensions of both

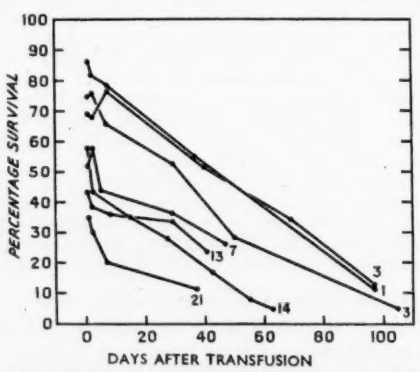

Fig. 1—Post-transfusion survival of red cells stored at —20°C in trisodium citrate/glycerol (solution I). In this figure and in figs. 2 and 3 the numbers at the end of each curve indicate the period of storage in weeks.

stored and fresh cells were prepared. Serial dilutions of each antiserum were made in bulk, and then a small volume of each was mixed with an equal volume of the cell suspension to be tested. The reactions of the frozen cells were compared with those of the fresh cells on the same slide, both macroscopically and microscopically.

Results

RATE OF SPONTANEOUS HÆMOLYSIS IN VITRO

In experiments in which packed red cells from heparinised blood were mixed with citrate-glycerol solution and stored at —20°C the effect of varying the glycerol concentration and the citrate concentration was assessed.

When the final concentration of glycerol was 30% (*w/v*), the average percentage lysis after a year's storage was about 15%. Increasing the concentration of glycerol to 40% (*w/v*) produced no appreciable decrease in lysis. When the concentration of glycerol was lowered to 20% (*w/v*), there was an increase in lysis—namely, 6% lysis after three months' and 50% lysis after six months' storage.

After a year's storage no consistent differences were observed between mixtures containing concentrations of trisodium citrate varying from 2·6 to 3·2%. However, when part of the sodium citrate was replaced by citric acid, the rate of lysis was slightly diminished—e.g., in one experiment the average hæmolysis after a year in

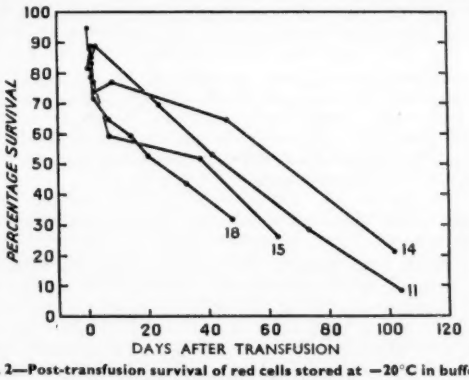

Fig. 2—Post-transfusion survival of red cells stored at −20°C in buffered tripotassium citrate/glycerol (solution III).

8 mixtures containing 2·9–2·3% trisodium citrate and 0·1–0·5% citric acid was 5·3% (range 3·7–6·3%) compared with 8·3% (range 7·9–8·6%) in 3 mixtures containing trisodium citrate alone. The substitution of 3% potassium citrate for 3% sodium citrate did not affect the rate of hæmolysis.

When the red cells were washed three times in saline solution before being mixed with trisodium-citrate glycerol and stored they did not hæmolyse more rapidly than unwashed cells in the same solution.

These results were all obtained with red cells from heparinised blood stored in small test-tubes. Additional information about the rate of spontaneous hæmolysis was obtained from estimations made on the bottles used for transfusion. Red cells stored in solution III for eleven to fifteen weeks showed less than 2·5% hæmolysis. Red cells stored in solution IV for up to nineteen weeks showed less than 3% hæmolysis; after from twenty-four to thirty-one weeks there was between 3% and 7% hæmolysis.

Red cells stored in dextran-citrate-plasma for sixteen weeks showed 7% hæmolysis; heparinised red cells stored for twelve weeks in the lactate-glycerol solution showed 44% hæmolysis. However, experiments in vitro undertaken subsequently showed that in a solution of sodium lactate and glycerol buffered with phosphates hæmolysis took place only slowly.

The figures for hæmolysis given so far refer to the mixtures immediately after thawing. During the "recovery" of the cells—i.e., the washing, first in decreasing concentrations of glycerol and subsequently in saline solution—further hæmolysis took place, but usually only about 5% in red cells stored in solutions I–IV. As mentioned above, the percentage recovery expresses the proportion of red cells actually available for transfusion compared with the number originally frozen. In solutions I–IV recoveries were usually about 90%; in solution IV recovery was estimated on 9 bottles, stored for eleven to thirty-one weeks, and the average was 91·5%.

In the unbuffered lactate-glycerol solution there was gross hæmolysis on thawing, followed by considerable further lysis on washing; thus, in the bottle stored for twelve weeks in which there was 44% hæmolysis on thawing, the final recovery was only 31%.

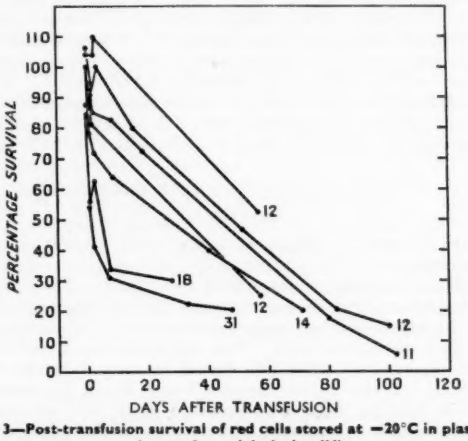

Fig. 3—Post-transfusion survival of red cells stored at −20°C in plasma-citrate-glycerol (solution IV).

SURVIVAL OF RED CELLS IN VIVO

Solution I (trisodium citrate/glycerol).—14 transfusions of blood stored for two days to twenty-one weeks were given; in 10 the red cells had been stored with 30% glycerol, and the survival of 7 of these is plotted in fig. 1. Note that viability diminishes rapidly during storage, with the result that after only three weeks at −20°C the percentage survival twenty-four hours after transfusion has fallen to 70%.

The twenty-four-hour survival of all 14 cases is shown in fig. 4. Note that the post-transfusion survival of red cells stored in 20% glycerol and 40% glycerol appears to be the same as that of the cells stored in 30% glycerol.

For comparison with results obtained with other solutions the average survival in 7 cases in which the period of storage was eleven to fourteen weeks is given in table I.

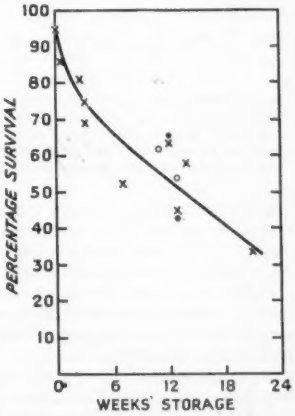

Fig. 4—Percentage survival twenty-four hours after transfusion of red cells stored at −20°C for various periods in trisodium citrate/glycerol (solution I). Crosses represent cases stored in standard solution, final glycerol concentration 30%; two circles are cases in which the glycerol concentration was 20%; and two solid dots cases in which glycerol concentration was 40%.

Solution II (tripotassium citrate/glycerol).—5 transfusions were given; the period of storage ranged from ten to fifteen weeks. The average post-transfusion survival is shown in table I for comparison with the survival of red cells stored for a similar period in the other solutions.

Red cells stored in solution II had a slightly higher average survival than red cells stored in solution I, but the difference was not significant.

Solution III (buffered tripotassium citrate/glycerol).—4 transfusions were given; the period of storage ranged from eleven to eighteen weeks. The survival of the red cells is illustrated in fig. 2, and the twenty-four-hour survival is also shown in fig. 5. The average survival of 3 cases in which the period of storage ranged from eleven to fifteen weeks is given in table I. It is evident that viability is far better maintained in this solution than in solutions I and II.

Solution IV (plasma-citrate-glycerol).—11 transfusions were given: 9 of red cells stored in solution IVa and 2 in solution IVb. The period of storage ranged from eleven to thirty-one weeks. There was little difference between the survival of the red cells stored in solution IVb and those stored in solution IVa, and the results are therefore

considered together. In 7 cases the survival of the red cells was followed for more than a week after transfusion, and the results in these 7 cases are illustrated in fig. 3. The percentage survival of all 11 cases at twenty-four hours after transfusion is shown in fig. 5. In addition the average post-transfusion survival of 6 cases in which the period of storage was between eleven and fourteen weeks is given in table I for comparison with the survival of red cells stored in the other solutions.

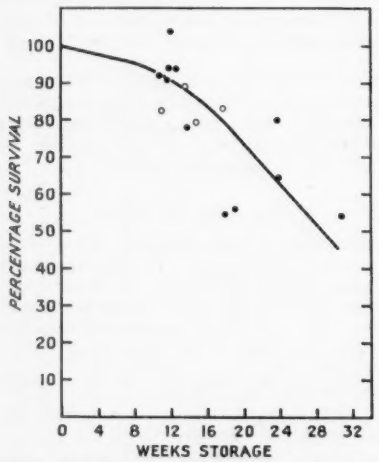

Fig. 5—Percentage survival twenty-four hours after transfusion of red cells stored at −20°C for various periods in plasma-citrate glycerol (solution IV), marked by solid dots, and in buffered potassium citrate/glycerol (solution III), marked by circles.

As fig. 5 shows, viability diminished only slightly during the first twelve or fourteen weeks' storage but thereafter diminished more rapidly. As fig. 3 shows, red cells stored for twelve to fourteen weeks often had a post-transfusion survival scarcely distinguishable from that of fresh red cells.

Other solutions.—A single transfusion of red cells stored in dextran-citrate-glycerol for sixteen weeks was given. The percentage survival twenty-four hours after transfusion was 70%.

3 transfusions of blood stored in lactate-glycerol solution (with added calcium) were given. In the first 2 cases, in which the periods of storage were nine and eleven weeks, the survival twenty-four hours after transfusion was about 80%. In the 3rd case, in which the red cells were stored for twelve weeks, survival was only 25%. No reason for this gross discrepancy was found. It did not seem worth while making further experiments with this solution in view of the rapid rate of spontaneous hæmolysis in vitro (see above).

EFFECT OF WASHING ON SURVIVAL OF RED CELLS

Fresh Red Cells Washed in Saline Solution

2 transfusions were given of fresh red cells washed seven times in 0·85% unbuffered saline solution. In the 1st case the red cells were from blood which had been taken into A.C.D. solution and kept ten hours at +4°C; in the 2nd case the blood was taken into heparin immediately before being washed. At twenty-four hours the survival figures were 100% and 101% respectively; at forty-eight hours 100% and 95%; and at twenty-eight days 79% and 69%. It was concluded that seven washes in physiological saline solution did not affect the viability of fresh red cells.

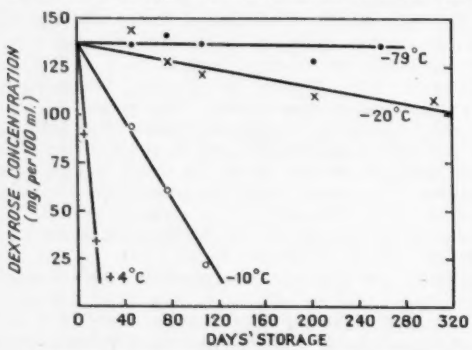

Fig. 6—Estimates of dextrose concentration in red cells mixed with citrate/glycerol (solution I) after various periods of storage at +4°C, −10°C, −20°C, and −79°C.

Stored Red Cells Washed in Citrate Solutions of Different pH

A second experiment was made to discover whether the survival of stored red cells was affected by the pH and dextrose content of the solution in which they were washed. Two bottles of stored red cells were mixed, and the red cells were then put in two separate bottles. The red cells in one bottle were washed in the ordinary solutions (a) of glycerol in 3% trisodium citrate (pH 7·7, dextrose nil). Those in the second bottle were washed in solutions (b) to which one part in twenty of A.C.D. solution was added to give a pH of 6·9 and a dextrose content of 0·125%. In the actual experiment two bottles of group-AN red cells stored for sixteen months at −79°C were pooled and then divided into two lots and washed differently as described; two bottles of group-OM red cells stored for six months at −20°C were treated in the same way.

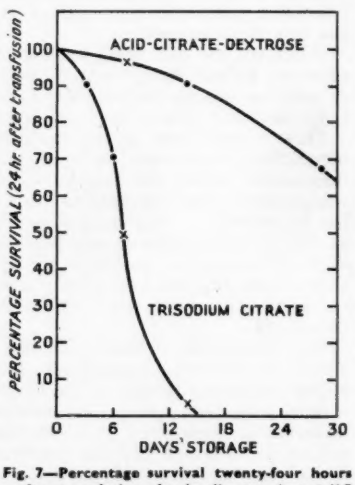

Fig. 7—Percentage survival twenty-four hours after transfusion of red cells stored at +4°C for various periods in trisodium citrate and in A.C.D. solution. Crosses are from data published by Ross et al. (1947) and solid dots from data assembled by Mollison (1951).

The red cells were then transfused as follows: one patient received group-AN cells washed in solutions (a) and group-OM cells washed in solutions (b); the second patient received group-AN cells washed in solutions (b) and group-OM cells washed in solutions (a). This plan was adopted to eliminate systematic errors due to differences between recipients. The mean percentage survival of the cells washed in solutions (a) was the same as that of the cells washed in solutions (b). It was concluded that there was no advantage in adjusting the pH of the wash solutions from 7·7 to 6·9 or in adding dextrose to them in a final concentration of 0·125%.

GLYCEROL CONCENTRATION IN WASHED RED-CELL SUSPENSION

In 10 cases a sample of the red-cell suspension used for transfusion was centrifuged and the glycerol concentration of the supernatant fluid determined. Preliminary observations had shown that the glycerol concentration of the whole red-cell suspension was very close to that of its supernatant fluid. The glycerol concentration in the supernatant fluid was found to vary between 0·01 and 0·1%, the higher figures being found in cases in which the red cells had received only two washes in saline solution (following the washes in decreasing concentrations of glycerol, as described above), and the

lower figures in cases in which three washes in saline solution had been given. No correlation was observed between glycerol concentration and red-cell survival.

CELL VOLUME, INTRACELLULAR CATION CONCENTRATION, AND OSMOTIC FRAGILITY

Red cells mixed with glycerol-citrate solutions show some initial swelling, amounting to about 20% in solution I. This swelling is maximal within an hour; thereafter the cells begin to shrink, but at the end of twenty-four hours they are still about 10% above their original volume. During storage at −20°C there is progressive shrinkage, which is associated with a loss of total base and a decrease in osmotic fragility. By the end of about a month red cells mixed with solution I have shrunk to about 80% of their original volume and have lost about 50 m.eq. of base per litre of cells. Little further change takes place during a further five months' storage. Some examples of the changes observed in red cells stored for three months in solutions I–IV are given in table II.

Measurements of sodium transport on red cells stored three months in solution I were kindly made by Prof. M. Maizels and Dr. E. J. Harris. It was found that the sodium transport was substantially normal but that cell permeability was increased. In a second estimation cells stored five months in solution I were examined; these cells showed little change in active sodium transport but, again, were much more permeable than normal.

DEXTROSE CONSUMPTION

Fig. 6 shows the results of estimates of dextrose concentration after various periods of storage at different temperatures The rates of disappearance of dextrose in this experiment, expressed as mg. per g. of hæmoglobin a day, were calculated to be as follows:

At +4°C 0·62; at −10°C 0·084; at −20°C 0·008; at −79°C probably nil.

In a second experiment (not shown in fig. 6) the figures were as follows:

At −10°C 0·067; at −20°C 0·006; at −79°C probably nil.

Since it is of considerable interest to know whether dextrose concentration does diminish in red cells stored at −20°C the correlation coefficient for the observations shown in fig. 6 was calculated: −0·784, S.E. 0·378; hence $0{\cdot}02 < P < 0{\cdot}05$.

In a further experiment the rate of dextrose consumption in mixtures containing respectively 25% and 50% glycerol (final concentrations) was compared. During storage at −20°C the mixtures containing 25% glycerol were solid, and those containing 50% glycerol were liquid. During a period of four months the consumption of dextrose did not differ significantly in the two mixtures.

PRESERVATION OF RED-CELL ANTIGENS

Tests were made to detect the following red-cell antigens in blood stored for a year at −20°C: A, B, M, N, S, D, C, c, E, P, Lu, Le^a, Le^b, K, and Fy^a. In all cases these antigens were still detectable, although the reactions were weaker than those given by fresh cells. There was considerable variation between blood samples: for instance, in some a particular antigen seemed to have deteriorated after three months' storage, whereas in others this antigen seemed almost unimpaired after a year's storage. It seems likely that the A antigen and the antigens of the Rh system deteriorate less rapidly than antigens of the other blood-group systems.

Discussion

The present results show that in an appropriate medium—e.g., solutions III and IV—red cells stored at −20°C not only undergo very little hæmolysis during three months but retain, almost unimpaired, the ability to survive after transfusion. With longer periods of storage post-transfusion survival diminishes progressively. In other media—e.g., solutions I and II—red cells stored at −20°C show a progressive diminution in post-transfusion survival from the very beginning of the storage period. This pattern of survival of red cells stored in different solutions at −20°C strongly recalls the pattern observed in different solutions at +4°C; this is illustrated by comparing figs. 4 and 5 with fig. 7.

Note that in A.C.D. solution at +4°C and in solutions III and IV at −20°C there is only a slight loss of viability for an initial period (fourteen days at +4°C, and fourteen weeks at −20°C). Thereafter viability diminishes at an increased rate. By contrast, in trisodium-citrate solution at +4°C and in solution I at −20°C viability is lost rapidly from the beginning of the storage period. It does not seem likely that this big difference in behaviour in the different solutions can be explained by a slowing of chemical processes in the "favourable" solutions. It seems more probable that the rapid loss of viability in trisodium-citrate solution, both at +4°C and at −20°C, is due to physical damage. Lovelock (1954) estimated the lipid content of red cells stored for fourteen weeks in solutions I and IV and found that in solution IV there was no loss of cell lipids, whereas in solution I about 30% of the cell lipids was lost.

It seems likely that the damage observed in red cells stored in solutions I and II is due to the alkalinity of these mixtures. In the two solutions (III and IV) in which viability is well maintained at −20°C buffer systems are present: potassium dihydrogen phosphate and dipotassium hydrogen phosphate in solution III, and trisodium citrate and disodium hydrogen citrate together with a relatively large volume of plasma in solution IV.

Possibly further improvement in the maintenance of viability at −20°C could be obtained by modifying one of the solutions described here—e.g., the optimal pH may be different from that of the present mixtures. However, the fact that chemical change takes place at −20°C, shown by the consumption of dextrose, suggests that preservation for an indefinite period cannot be expected at this temperature.

In this connection some results published previously by Ross et al. (1947) are of the greatest interest. The survivals in vivo of red cells stored in Alsever's solution at 25°C and at 4°C were compared. The period of storage after which post-transfusion survival decreased to 50% was just under three days at 25°C and about seventeen days at +4°C—i.e., a fall in temperature of 21°C was associated with about a sixfold lengthening of the period during which the red cells maintained 50% viability. If the process responsible for the loss of viability were chemical, it would be expected that storage at −20°C—i.e., 24°C lower than +4°C—would lengthen the storage period rather more than sixfold. Fig. 5 shows that the viability of red cells stored in solution IVa at −20°C decreases to 50% after about thirty weeks. The viability of red cells stored at +4°C in A.C.D. solution decreases to 50% after about thirty-five days (fig. 7). Thus it seems that viability is maintained about six times as long at −20°C as at +4°C. This is shown in another way by figs. 5 and 7, from which it will be seen that the loss of viability is very slow for fourteen days in A.C.D. at +4°C, and for about fourteen weeks in solution IV at −20°C; thereafter in both solutions the rate of loss of viability rises.

The results of only 4 transfusions of red cells stored at −20°C have previously been reported. Mollison et al. (1952) transfused red cells stored for twenty-nine, seventy-seven, and eighty-four days; in addition to the period of storage at −20°C the red cells had been kept ten days at +4°C. Survival at twenty-four hours was 75–95% (average 82%), and the remaining cells dis-

appeared at about 1% a day. These red cells were stored in a mixture of their own plasma containing a proportion of A.C.D. solution and glycerol-saline solution. Although viability was well maintained in this solution, relatively rapid hæmolysis took place during storage, and it was for this reason that citrate was substituted for saline solution in the present solutions. Brown and Hardin (1953), who gave a transfusion of red cells stored fifty days in glycerol-lactate at —15°C, found a post-transfusion survival of about 50% and thought that the post-transfusion loss of red cells was due to failure to remove all the glycerol from the cells. However, the present results make it seem more likely that the loss was due to physical damage to the red cells during storage.

The results in table II show that red cells stored in sodium citrate (solutions I and IV) contain more sodium than potassium, whereas those stored in potassium citrate contain more potassium than sodium. It appears that the ratio of sodium to potassium does not affect survival in vivo, although there appears to be an association between total base content and viability. A reduction in cell volume, a loss of base, and a decrease in osmotic fragility appear to be associated with one another.

Cell shrinkage and loss of base do not seem to be due solely to the concentration of citrate in the medium. For example, cells stored for fourteen weeks in solution IVb, which has almost the same citrate content as solution I, show less shrinkage and a smaller loss of base than do cells stored in solution I. This difference may be due to the fact that cells stored in solution I suffer more physical damage than do cells stored in solution IV, or to the fact that solution IV contains some penetrating anions (Cl^-).

As mentioned above, there is some evidence that red cells stored in solution I become abnormally permeable to cations. Experiments have not yet been made to determine whether this permeability is reduced in solutions III and IV. Meanwhile it seems likely that the increased permeability is further evidence of physical damage occurring in solution I.

Although it may not be possible to maintain the viability of red cells for more than a few months at —20°C, even in buffered glycerol mixtures, it is of practical importance to know that the red-cell antigens are still detectable after at least a year's storage at this temperature. Grove-Rasmussen et al. (1953) have reported that red cells stored for twenty weeks in trisodium citrate at —20°C react as well as fresh cells. Our results suggest that there is considerable variation and that some antigens (such as P) undoubtedly deteriorate during this period and may not be detectable with weak antisera. However, many of the antigens are relatively well preserved and, in a laboratory where potent sera are used for genotyping, it has been found very convenient to keep a panel of cells of known groups readily available in a —20°C refrigerator.

In the present work on storing red cells for blood-grouping tests, only trisodium citrate/glycerol solution (solution I) was used. It is likely that better results would be obtained by using a solution—such as one with buffered phosphate (solution III)—in which red-cell viability is better maintained.

Summary

Red cells stored at —20°C in a solution of trisodium citrate (3%) and glycerol (30%) undergo only slow hæmolysis, but they rapidly lose their ability to survive after transfusion.

In modified citrate-glycerol solutions, the essential feature of which is probably the presence of buffers, survival is maintained, almost unimpaired, for about three months. Thereafter viability diminishes with time; after thirty weeks' storage only about 50% of the red cells survive after transfusion. This slow loss of viability may be due to the fact that chemical change is not arrested at —20°C, and it is demonstrated that dextrose is in fact slowly utilised under these conditions.

Red cells stored for a year at —20°C in unbuffered citrate-glycerol mixtures react specifically with blood-grouping sera, although their reactions may be weaker than those of fresh cells.

We wish to thank Dr. J. D. James, Dr. P. D. Booth, and Dr. G. Plaut, of the North London Blood Transfusion Centre, for making blood available. Lederle Laboratories, New York, supplied the anti-M serum.

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ORAL PENICILLIN

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THE necessity for parenteral injection has been one of the major disadvantages of penicillin, and repeated attempts have been made to devise effective oral preparations. Trials with earlier products proved unsatisfactory because of poor and irregular absorption in spite of large dosage; so, supplies of penicillin being strictly limited, the oral route was not considered a practical proposition. Since then there has been a tremendous increase in the production of penicillin, with a great reduction in cost, and oral administration has been subjected to frequent investigation.

Benzathine penicillin, a new insoluble compound (N : N'-dibenzylethylenediamine dipenicillin G, known also as D.B.E.D. penicillin and benzethacil) has recently been produced, and preliminary tests by the oral route suggest that it gives reliable, effective, and prolonged blood-penicillin levels, particularly in children. As a result of these claims considerable interest has again been aroused in oral penicillin, and many different preparations are now available.

Controlled trials have so far been limited, but nevertheless the results have tended to be inconsistent:

Finberg et al. (1953) obtained excellent clinical results by treating pneumococcal and hæmolytic streptococcal infections in children with benzathine penicillin.

Coriell et al. (1953) reported good results, as well as satisfactory blood-penicillin levels, in the treatment of scarlet fever in children with the same compound.

Cathie and MacFarlane (1953) found some absorption of penicillin after a single dose of 300,000 units of benzathine penicillin in all of 118 people, of whom 101 were children.

Bayne et al. (1953) gave a single dose of 300,000 units of benzathine penicillin to 6 adults and found detectable blood-penicillin levels for four hours but not after six hours; and after a dose of 600,000 units, only 1 of 6 adults lacked a blood-penicillin level of 0·03 unit per ml.

Foltz and Schimmel (1953) showed that, after the administration of single doses of 300,000 units to the same 12 adults, higher blood-penicillin levels were obtained with potassium penicillin G and procaine penicillin than with benzathine penicillin, and that, with each preparation, penicillin was absent from some serum samples at the end of six hours.

Wright et al. (1953) gave tablets of different oral preparations to the same 12 persons in a dosage of 200,000 units and found that absorption was more consistent with buffered potassium penicillin G than with benzathine penicillin.

Welch et al. (1953) estimated the blood-penicillin levels of ambulant adults at intervals after oral administration of benzathine penicillin in tablet form. Penicillin was usually detected for two or three hours after a dose of 200,000 units; with larger doses, up to 750,000 units, absorption was more consistent, and the blood-penicillin levels tended to be higher and more prolonged; there was, however, considerable individual variation in the amount of absorption, levels of only 0·012 unit per ml. being recorded in some cases.

In view of these irregular results it seems important that further information should be obtained about oral penicillin, so that its scope and limitations can be more clearly defined. Consequently we made tests, mainly in adults, to determine particularly the degree of absorption after a single dose of various oral preparations; at the same time we undertook a few clinical trials.

Methods

The various preparations were usually given before breakfast, and in many instances the dose was accurately measured. At times teaspoons were used, but these vary considerably in capacity, moderate to large types usually holding 3–5 ml., and accurate dosage is impossible; but in this trial there was usually a close approximation to the desired amount.

Samples of blood were collected at definite intervals, and the blood-penicillin levels were estimated by a standard serial-dilution technique using *Staphylococcus aureus* (Oxford) as the test organism. When any delay in making the tests was likely, the serum was kept in the refrigerator until required.

Results

Previous findings indicate that there is considerable individual variation in the amount of absorption after the oral administration of penicillin. It was consequently considered that more valuable information would be obtained by making single estimations in a large number of people rather than by making many estimations in a few. This was the main object of the investigation, and 330 tests have been made on patients and volunteers.

TABLE I—BLOOD-PENICILLIN LEVELS AFTER A SINGLE DOSE OF BENZATHINE PENICILLIN

Group	Dosage (units)	Time after dose (hr.)	Blood-penicillin (unit per ml.)							No. of persons
			None detected	0·03	0·06	0·125	0·25	0·5	1 or more	
Adults	300,000	2–3	4	5	2	8	1	0	0	20
		5	3	3	1	3	0	0	0	10
	600,000	1–3	1	10	14	18	19	5	1	68
		5–6	11	11	23	13	1	0	0	59
Children	300,000	2–3	0	0	0	0	8	2	0	10
		4–6	0	2	3	1	1	1	2	10
	600,000	3	0	2	5	2	2	0	0	11
									Total	188

TABLE II—BLOOD-PENICILLIN LEVELS IN ADULTS AFTER A SINGLE DOSE OF SOLUBLE PENICILLIN G

Dosage (units)	Preparation	Time after dose (hr.)	Blood-penicillin (unit per ml.)							No. of persons
			None detected	0·03	0·06	0·125	0·25	0·5	1 or more	
300,000	Eskacillin	1–3	1	3	5	6	5	2	5	27
		4–6	2	3	2	3	0	2	0	12
	Pradupen	1–3	0	0	0	0	0	1	0	1
		4–6	0	1	3	3	2	0	0	9
600,000	Eskacillin	1–3	0	1	5	4	17	11	8	46
		4–6	0	5	8	10	4	1	2	30
	Pradupen	1–3	0	0	0	0	2	5	5	12
		4–6	1	3	1	0	0	0	0	5
									Total	142

Two distinct types of oral penicillin have been used: (1) the insoluble benzathine penicillin ('Penidural,' Wyeth); and (2) soluble compounds: (*a*) potassium penicillin G ('Eskacillin,' Menley & James), and (*b*) potassium salt of benzylpenicillin *B.P.* ('Pradupen,' Evans Medical Supplies).

BENZATHINE PENICILLIN

Penidural is a stable and palatable suspension, which is well tolerated. A single dose of 300,000 or 600,000 units was given to 181 people (150 adults and 31 children). Usually, only one sample of blood was taken from each person; it was collected either two or three hours after oral administration which is considered to be the peak period of absorption, or after five or six hours (table I).

There was no uniform pattern of absorption, and the blood-penicillin levels showed considerable individual variation irrespective of the dosage.

In adults a dose of 300,000 units gave disappointing results and was discontinued because occasionally there appeared to be little or no absorption. Better results were obtained with a dosage of 600,000 units. A detectable blood-penicillin level was found within three hours of administration in 67 of 68 assays, and in 6 instances a level of 0·5 unit per ml. or more was obtained. After five or six hours 37 of 59 persons still had levels of 0·06 unit per ml. or more.

Only a limited investigation was made in children, but the results were more striking: evidence of absorption was found in all the cases, and 2 young infants had 1 or 2 units per ml. from four to six hours after a dose of 300,000 units. A dose of 600,000 units did not produce any increase in the blood-penicillin levels.

These irregular results are not surprising, because penidural is an insoluble compound and probably has to be broken down in the alimentary tract to liberate a soluble form of penicillin G. The precise mechanism of the reaction has not been determined, but Lozinski and Gleason (1953) consider that the complex penicillin compound undergoes rapid hydrolysis in normal gastric juice and some hydrolysis in an alkaline medium. Considerable individual variation might therefore be found in not only the release of soluble penicillin from the compound but also its subsequent absorption.

In some cases blood-penicillin levels were estimated five or six hours after a second or third dose of 600,000 units, and evidence of a cumulative response was usually, but not invariably, found.

11 men with acute gonorrhœa were treated with penidural. 2 of them each received one dose of 600,000 units; there was an immediate improvement, but both cases relapsed. 9 of them were given a second dose of

600,000 units after an interval of six hours; 7 of these were cured, and 2 relapsed.

SOLUBLE COMPOUNDS

The two compounds eskacillin and pradupen are similar preparations which vary slightly in composition and method of preparation. Eskacillin is crystalline potassium penicillin G which, when required for use, is dissolved in a special flavoured and buffered solution. It is palatable and, at room-temperature, retains its potency for at least seven days. Pradupen is a powder containing potassium benzylpenicillin as well as buffering and flavouring agents; solution is effected by the addition of tap-water.

These preparations were given to 142 adults, and the resulting blood-penicillin levels are given in table II.

Irregular readings were again obtained in a similar group of adults; but usually absorption was quicker and blood-penicillin levels tended to be higher than with penidural.

With a dose of 300,000 units high blood-penicillin levels (1 unit per ml. or more) were obtained at the peak period in a few cases, but in 1 instance absorption was not detected, and on several occasions levels of 0·03 unit per ml. were found. Better results were produced by increasing the dose to 600,000 units, when all the 58 persons gave evidence of absorption at the peak period, the range varying from 0·03 to 1 unit per ml. With eskacillin some penicillin was still present in all of 30 cases at the end of from four to six hours.

15 male cases of acute gonorrhœa were each treated with two doses of 600,000 units, the second dose being given after an interval of six hours; all showed rapid improvement, but with eskacillin 2 of 7 cases relapsed. Another case was treated with pradupen in two doses of 400,000 units, with an interval of six hours, but relapsed after an initial improvement.

Discussion

It is generally accepted that a variable, and sometimes small, proportion of penicillin is absorbed after oral administration, and consequently this route is not recommended in the initial stages of acute severe infections. These views are supported by the results of the present investigation. Absorption after oral dosage was irregular, irrespective of the nature of the penicillin compound or the age of the recipient.

The present work was mainly concerned with adults, in whom a dose of 300,000 units gave disappointing results. In a few instances there was no evidence of absorption, and in some cases the absorbed penicillin was eliminated within six hours. Better results were given with a dose of 600,000 units, but there was again found considerable inconsistency not only in the peak blood-penicillin levels but also in the persistence of penicillin in the blood. In the great majority of tests made up to three hours after administration—i.e., the peak period—blood-penicillin levels of at least 0·03 unit per ml. were obtained, and in many of them considerably higher levels were found.

It is often stated that 0·03 unit per ml. represents the minimal effective level of penicillin, but this figure has little, if any, therapeutic significance. It can be readily demonstrated by in-vitro tests that, with moderate numbers—e.g., 2,000,000 per ml.—of a sensitive strain of *Staph. aureus*, a level of 0·03 unit per ml. of penicillin has merely a transient bacteriostatic effect, whereas a level of 0·3 unit per ml. has considerable bactericidal activity. With a pneumococcus, which is a highly sensitive organism, a level of 0·03 unit per ml. may, however, have some bactericidal effect.

The blood-penicillin level is not a direct index of therapeutic activity, because many other factors, including the sensitivity and accessibility of the infecting organisms, must also be considered. There is, however, little doubt that, in most acute infections, levels of 0·03 unit per ml. are likely to have limited therapeutic activity.

In the present investigation blood-penicillin levels of 0·03 unit per ml. or less have been obtained in each group of subjects with all the preparations used; moreover it is impossible to predict when absorption is likely to be so small. It must therefore be emphasised that in the treatment of acute infections, even with sensitive organisms, the initial doses of penicillin should be given parenterally to ensure rapid bactericidal activity. When the clinical response to parenteral penicillin is satisfactory, continuation treatment with oral preparations should prove adequate in most cases; this form of therapy should be particularly advantageous in children, in whom parenteral injection may be a very disturbing experience. Oral administration may also prove useful when the prophylactic use of penicillin is considered advisable.

It has been shown that, by combination with probenecid, which delays the renal excretion of penicillin, oral products give consistently higher and more prolonged levels. Severe reactions to penicillin are becoming a serious problem; and, though oral administration reduces, but does not eliminate, this risk, the combination of penicillin with another potential sensitising agent may not be entirely beneficial.

The main advantage of oral penicillin is convenience of administration; but, even with the new products, there still remains the serious objection of irregular, and sometimes poor, absorption, particularly in adults. It must also be realised that oral administration constitutes a relatively expensive form of penicillin therapy. A dosage of 300,000 or 600,000 units six-hourly costs considerably more than a daily injection of 400,000 units of procaine penicillin, which gives similar, but more uniform, blood-penicillin levels (Fairbrother and Daber 1950).

The increasing number of potent antibiotics, the great variety of proprietary preparations, and the potential dangers of these agents necessitate a careful assessment of each case before advising any form of antibiotic therapy. It is therefore important that convenience of administration should not lead to widespread and indiscriminate use of oral penicillin, especially in the treatment of minor infections.

Summary

Blood-penicillin levels have been estimated on 330 occasions after the oral administration of various preparations of penicillin.

A single dose of 300,000 units gave disappointing results in adults.

Absorption was more consistent after a dosage of 600,000 units, but considerable variation was found in the amount absorbed by different people.

It is a pleasure to thank our medical colleagues and the nurses for their ready coöperation throughout this investigation. Messrs. J. Wyeth & Brother Ltd., Menley & James Ltd., and Evans Medical Supplies Ltd. supplied the oral preparations of penicillin.

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BENZATHINE PENICILLIN BY MOUTH IN CHILDREN

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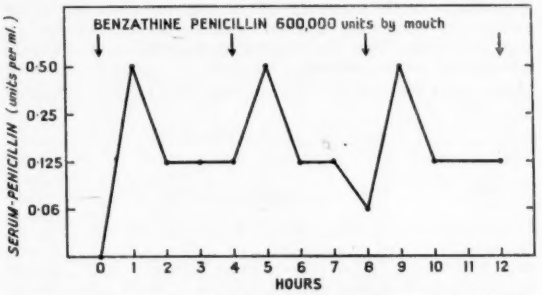
AN effective, reliable, and inexpensive oral penicillin preparation is much to be desired. N,N'dibenzylethylenediamine penicillin (benzathine penicillin or 'Penidural'), which has been suggested as such a preparation, is a sparingly soluble compound of penicillin first described by Szabo et al. (1951) and Seifter et al. (1951). Lepper et al. (1952) estimated the blood-penicillin levels obtained after the oral administration of benzathine penicillin to children aged less than 5 years and found blood-penicillin levels of not less than 0·03 unit per ml. of serum in five of seven children six hours after the administration of 250,000 units. Coriell et al. (1953), who administered benzathine penicillin to nine children aged 4–11 years in a dosage of 7000 units per kg. body-weight, reported that none of them had a serum-penicillin level as high as 0·03 unit per ml. at six hours. Cathie and MacFarlane (1953) showed that benzathine penicillin 300,000 units, given orally to 95 children weighing 10–70 lb., produced a serum-penicillin level of not less than 0·03 unit per ml. three hours after administration. The serum-penicillin levels at four and six hours after administration were not recorded.

The trial of benzathine penicillin reported here was planned to establish for children a scheme of dosage,



Serum-penicillin levels with repeated doses of benzathine penicillin 600,000 units four-hourly in a child weighing 40 lb.

based on body-weight, which would maintain a constant serum-penicillin level of at least 0·03 unit per ml.

Materials and Method

Penicillin-serum levels were estimated by a capillary technique using a strain of *Streptococcus pyogenes* as the assay organism.

Assays were made in each child before the start of treatment to ensure that there was no penicillin present in the serum.

Benzathine penicillin was given, irrespective of mealtimes, in single doses of 5, 10, 15, and 20 ml. (5 ml. = 300,000 units of penicillin) to children in different weight-groups, and serum-penicillin levels were estimated at regular intervals up to six, eight, or twelve hours after its administration. The possible cumulative effect of repeated six-hourly doses on the serum-penicillin level was also studied.

Results

The minimal satisfactory serum-penicillin level was taken as 0·03 unit per ml.

Benzathine penicillin was rapidly absorbed, and satisfactory serum-penicillin levels were found an hour after administration. Thus the dose which at six hours produced satisfactory serum-penicillin levels produced at an hour in 28 of the 30 patients serum-penicillin levels of 0·125–1·000 units per ml. From three to six hours the serum-penicillin levels fell steadily.

The results summarised in table I show that 300,000 units of benzathine penicillin maintained a satisfactory serum-penicillin level for four hours in children weighing up to 40 lb., and for six hours in children weighing up to 25 lb.; and 600,000 units of benzathine penicillin was needed to maintain a satisfactory serum-penicillin level

TABLE I—PENICILLIN-SERUM LEVELS AFTER ADMINISTRATION OF ORAL BENZATHINE PENICILLIN

Dose (units)	Interval after administration (hr.)	Weight range (lb.)	Patients showing satisfactory serum-penicillin levels
300,000	4	0–40	19 of 19 (*100%*)
		<40	0 of 7 (*0%*)
	6	0–25	8 of 8 (*100%*)
		25–40	0 of 13 (*0%*)
600,000	4	40–70	16 of 17 (*94%*)
		<70	6 of 16 (*37%*)
	6	25–40	7 of 9 (*78%*)
		<40	6 of 29 (*24%*)
900,000	4	40–70	8 of 9 (*89%*)
	6	40–70	5 of 9 (*55%*)
		40–70	2 of 8 (*25%*)
1,200,000	4	<70	11 of 11 (*100%*)
	6	<70	8 of 11 (*82%*)
	8	<70	4 of 6 (*67%*)

for four hours in children weighing 40–70 lb., and for six hours in children weighing 25–40 lb. In heavier children even higher doses were needed to maintain satisfactory serum-penicillin levels throughout the six hours between doses. Serum-penicillin levels estimated in 6 patients during a course of treatment were not significantly higher than those obtained after a single dose of benzathine penicillin. A typical example is shown in the accompanying figure.

From the results in table I a scheme of dosage is suggested (table II). Six-hourly doses of benzathine penicillin should be about 12,000 units per lb. body-weight, and four-hourly doses about 8000 units per lb. body-weight.

With a few exceptions children liked the flavour of benzathine penicillin. It was not, however, free from side-effects. There were no rashes, but of 131 children treated with benzathine penicillin 26 had loose stools and 3 had some nausea and vomiting. In no case, however, were these symptoms really troublesome.

Summary

Benzathine penicillin was given by mouth to children of different ages, and serum-penicillin levels were estimated.

Benzathine penicillin 300,000 units ('Penidural' 5 ml.) maintained satisfactory serum-penicillin levels for four hours in children weighing up to 40 lb. and for six hours in children weighing up to 25 lb., and 600,000 units for four hours in children weighing 40–70 lb. and for six

TABLE II—SCHEME OF DOSAGE BASED ON BODY-WEIGHT FOR BENZATHINE PENICILLIN

Weight (lb.)	Interval between doses (hr.)	Units of benzathine penicillin (300,000 units = 5 ml.)
0–25	6	300,000
25–40	4	300,000
	6	600,000
40–70	6	900,000–1,200,000
>70	6–8	1,200,000

hours in children weighing 25–40 lb. Heavier children required correspodingly higher doses.

A scheme of dosage based on body-weight is suggested for children.

It is a pleasure to acknowledge the help and encouragement given to us by Prof. R. S. Illingworth and Dr. J. L. Emery. Messrs. John Wyeth Ltd. supplied the penidural.

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TREATMENT OF MOLLUSCUM SEBACEUM

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THE condition known alternatively as molluscum sebaceum, kerato-acanthoma, or molluscum pseudo-carcinomatosum is now an established entity becoming increasingly well recognised (MacCormac and Scarff 1936, Musso and Gordon 1950, Rook and Whimster 1950, Beare 1953). The treatment of these cases is still, however, not generally agreed on (Beare 1954, Halnan 1953, 1954, Gold 1954). Indeed molluscum sebaceum is a self-limiting self-healing condition, and it might be argued that any treatment is therefore unnecessary. Against this its natural course may last up to six months, during which time the patient is left with an unsightly ulcerating tumour; hence treatment would appear to be justifiable to limit the life-cycle of the tumour and procure early healing.

Diagnosis

The danger of mistakenly diagnosing and treating a squamous epithelioma as molluscum sebaceum has been emphasised (Halnan 1953, 1954). Such difficulties may arise during the first two months of the tumour's life—i.e., before the formation of the central keratin plug. An adequate and representative biopsy specimen, however, examined by a pathologist familiar with the histological structure of molluscum sebaceum, taken in conjunction with the clinical history and findings, should make the diagnosis certain, in all cases. There is no doubt, however, that in the past many of these cases have been treated as squamous epitheliomata; hence statistics of treatment of epitheliomata should be reviewed in the light of recent knowledge. Once the keratin plug has been formed, the diagnosis is usually obvious clinically. If any doubt persists, the histological findings will once again be confirmatory. In short, the difficulties of diagnosis in these cases should be dealt with as for basal-cell carcinoma, squamous papillomata, or other conditions which may be confused with squamous epitheliomata—i.e., if in doubt biopsy and if necessary re-biopsy, rather than if in doubt treat all as epitheliomata.

Treatment

There appears to be two main methods of treating this condition: surgical removal, and radiotherapy.

SURGICAL REMOVAL

Surgical procedures have included diathermy or electrolysis, local excision and suture, and excision or curettage of the superficial parts of the tumour followed by cautery or application of caustics to the base.

MacCormac and Scarff (1936), describing their original 10 cases, recommended electrolysis followed by the application of carbon-dioxide snow. There were no recurrences among these cases.

Beare (1953) reports on treatment by combined curettage and diathermy in 76 cases with excellent cosmetic results. In 27 of these cases curettage was followed by a single exposure of superficial X rays in a dosage of 800–1200r. This post-operative irradiation has now been abandoned because "there is little if any advantage in giving X rays in addition to curettage." One case was noted in this series which had recurred after previous diathermy.

I. W. Whimster (personal communication) reports on 40 cases treated at St. Thomas's Hospital by surgical excision under local anæsthesia. Many of these lesions were unduly large, compared with the maximum of 1·0–1·5 cm. in diameter cited by Beare (1953).

RADIOTHERAPY

The treatment of molluscum sebaceum by radiotherapy has been likened to "using a sledgehammer to drive in a nail" (Beare 1954), and has been criticised on the grounds that large doses of either radium or X rays have to be used. The earliest cases of molluscum sebaceum were referred to the radiotherapy department at St. Thomas's Hospital in 1949, when the condition was not so well recognised and little was known about the preferential form of treatment. It was felt that treatment by radiotherapy alone could play a part in the treatment of the condition just as in other benign skin lesions—e.g., hæmangiomata, keloid scars, and plantar warts—and without resorting to a "sledgehammer" dosage. It was therefore in an attempt to determine the optimum dosage to cause regression of the tumour that the following 25 cases were treated by radiotherapy alone.

Technique

Identical methods were used in treating all the cases. A Chaoul tube was used delivering X rays at a voltage of 60 kV, 4 mA, and a half-value layer of 3·3 mm. of aluminium. The volume of tissue irradiated was confined to an amount just wide of the lesion. The treatment was given as a single exposure but in varying dosage. After treatment the area treated was inspected weekly or fortnightly so that the degree of reaction and the rate of regression of the tumour could be assessed. In 6 of these cases treated by varying dosage a biopsy specimen

RESULTS OF RADIOTHERAPY

Case no.	Dose (r)	Degree of reaction †	Tumour-regression time (weeks)	Reaction-regression time (weeks)
Group A:				
1	2500	3	4	8
2	2500	3	3	8
3	2500	3	4	7
4	2250*	3	3	6
Group B:				
5	2000	3	4	7
6	2000	2	4	5
7	1800	2	4	5
8	1750*	2	3	6
9	1750	2	4	5
10	1750*	2	3	4
Group C:				
11	1500	2	5	6
12	1500	2	5	6
13	1500	2	4	4
14	1500	2	4	4
15	1500	2	3	4
16	1500	2	3	4
17	1500	2	4	4
18	1500	2	4	4
19	1500*	2	4	4
20	1500	2	3	3
21	1500	2	3	3
Group D:				
22	1250*	1	8	4
23	1250*	1	8	3
24	1250	1	6	4
25	1200	1	6	4

Average tumour-regression time in groups B and C = 4 weeks.
Average reaction-regression time in groups B and C = 4½ weeks.
* Cases subjected to post-irradiation biopsy.
† 1, erythema only.
2, erythema + dry scaling.
3, erythema + vesicle formation + ulceration.

was taken of a representative portion of the tumour a week after irradiation and submitted to histological examination.

Results

Of the 25 cases of molluscum sebaceum treated by radiotherapy alone 5 had been treated by other methods previously. 1 case had been treated on three separate occasions: twice by local excision, and once by application of carbon-dioxide snow. 2 other cases had recurred after local excision on one occasion each, and of 2 other recurrences 1 had followed local applications of caustics and the other removal by diathermy.

The accompanying table shows the dosage given, the degree of reaction, and the length of time taken until the tumour had regressed completely and the reaction healed. In all the cases the cosmetic result has been good, leaving a typical flat slightly depressed scar. No recurrence has yet been noted after radiotherapy alone. An attempt has been made to assess these results from two aspects: (1) the rate of tumour regression correlated with the quantity of irradiation and hence also with the reaction produced; and (2) in cases subjected to post-irradiation biopsy, the quantitative cytological changes resulting, correlated with the quantity of radiation given.

From the table it will be seen that there are four separate dosage levels:

Group A.—A dosage equivalent to that used in treating squamous epitheliomata—2250–2500r. In all the cases the reaction was severe, labelled as 3rd degree, and because of this the rate of regression of the tumour was difficult to assess accurately. The reaction subsided in 6–8 weeks and tumour regression was complete by 4 weeks.

Group B.—A "subradical" dose was given—1750–2000r. The resulting reaction was less, being 3rd degree in only 1 case, and 2nd degree in the remainder. Tumour regression was complete in 4 weeks, and reaction healing lasted correspondingly shorter than in group A and was complete in 4–6 weeks.

Group C.—The dosage given was 1500r. The reaction was 2nd degree only and had settled within 3–6 weeks. Tumour regression took place within 3–5 weeks.

Group D.—The dosage used was roughly half that given for the radical treatment of squamous carcinomata—1200–1250r. The reaction was 1st degree in all the cases, being healed in 3–4 weeks. The rate of tumour regression was, however, appreciably slower than in the preceding groups, taking 6–8 weeks to be completed.

The average tumour-regression time for all the groups was about $4^1/_2$ weeks, and for groups B and C about 4 weeks. The average reaction-regression time for all the groups was about 5 weeks, and for groups B and C about $4^1/_2$ weeks.

This analysis shows that at the extremes of dosage levels the resultant tumour regression/reaction ratio is disproportionate. In group A the reaction produced was excessive, the dose level being too high. In group D the tumour-regression rate was appreciably slower, suggesting that the dosage was too low. The optimal range of dosage producing a satisfactory tumour-regression rate without an excessive degree of reaction therefore seems to be that used in groups B and C—i.e., 1500–1750r. The 1500r dose produced slightly less reaction than the higher dosages, and this therefore seems to be a satisfactory dosage. In bulkier lesions probably the larger dose of 1750r should be used.

Attempts to correlate cytological response with dosage have been more difficult because of the small numbers dealt with. In 6 cases biopsy specimens taken after irradiation at different dosage levels were submitted to histological examination, which showed that cytological changes due to irradiation were present in all specimens studied, but quantitatively there appeared to be little difference in the number of cells damaged irrespective of the dosage at 1250 or 2250r. It must, however, be emphasised that the numbers dealt with were small, and a larger series would have to be studied before a definite conclusion could be drawn.

Conclusions

Molluscum sebaceum may be effectively treated by radiotherapy. Histological examination after irradiation of these tumours suggests that there is little quantitative difference in cytological damage over a wide range of dosage. A satisfactory tumour-regression rate follows a dosage level of 1500–1750r. A dosage above this produces an unnecessarily more severe and prolonged reaction.

Summary

The diagnosis and results of various surgical treatments of molluscum sebaceum are reviewed.

The treatment of 25 cases by radiotherapy alone is reported, and the results are analysed.

Four groups of dosage levels were used and correlated with reaction and tumour-regression rate.

Correlation with cytological response in 6 cases showed little quantitative difference at various dosage levels.

I wish to thank Dr. J. A. C. Fleming, director of the department of radiotherapy, St. Thomas's Hospital, for his help and encouragement in publication, and Dr. I. W. Whimster for the histological reports on the biopsy specimens, and for permission to review his cases which were treated surgically.

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SPONTANEOUS RUPTURE OF THE BLADDER

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THIS case is recorded because of the rarity of spontaneous rupture of the bladder. The events took place in private practice in a small isolated community, with no ready source of reference, so I shall refrain from comment, other than to reiterate the admonitions of one of my late chiefs, "Watch the bladder," and to point out the relative harmlessness of non-infected urine spilt intraperitoneally, so long as it is removed at once.

A man, aged 65, slipped in the snow on Jan. 1, 1952, and injured his left hip. He crawled some distance to a road, where he was picked up by a passing lorry and brought into town.

Examination showed a fractured left femoral neck; this was confirmed by radiography on admission to hospital. He was put to bed, and traction was applied to the leg with adhesive plaster. During the period of delay before open reduction could be carried out (occasioned by seasonal lack of staff) the patient complained of difficulty in micturition, on one occasion only. On the afternoon of Jan. 2 he could not urinate; so the orderly was instructed to catheterise him, which he did with ease.

Operation.—On the morning of Jan. 6 open reduction of the fracture was done under spinal anæsthesia, and a Smith-Petersen nail was inserted in the usual manner.

Progress.—Next day exercises of the hip were started. Each day the patient appeared rather depressed and irritable, being worried about his heart, having been told on some previous occasion that it was weak. He had some difficulty in urinating and frequently asked for the bottle; but although he passed adequate quantities of urine, he must have had some retention. On the morning of Jan. 10 he developed severe epigastric pain after using the bedpan. When I saw him he was

shocked and in great discomfort. His abdomen was very tender and as hard as a board. Perforated peptic ulcer was diagnosed, and a long history of indigestion elicited to suit the diagnosis!

Laparotomy was done two hours later through an upper right paramedian incision. Much clear fluid was found, but no perforation, after diligent exploration of the stomach, although a sessile papilloma was found high up on the anterior surface. The possibility that the fluid might be urine was confirmed by feeling a small contracted bladder with a hole at its apex exactly like an old-fashioned ink-well. Through a lower midline incision a perforation was found on the posterior surface of the bladder about midway between its base and its apex. The bladder was opened through the retropubic space. The prostate was not enlarged, and the internal meatus appeared normal. The rent was sutured intravesically with interrupted catgut and reinforced intraperitoneally. The bladder was closed about a large rubber tube, a drain inserted to the retropubic space, and the incision closed in the usual manner. The gastric papilloma (which proved to be a leiomyoma) was excised with an inch margin of healthy stomach wall and the deficiency closed with two layers of continuous catgut.

Postoperatively I discovered that in 1944 the patient had undergone a transurethral resection for impaction of a stone in his urethra. Since then he had had no urinary symptoms. He was now treated by continuous gastric suction, intravenous fluid containing oxytetracycline, and 'flocillin D.S.' (a repository penicillin-streptomycin mixture). On Jan. 14 the gastric suction and the intravenous fluid were discontinued, and the patient began to take fluids by mouth. The flocillin was continued prophylactically until Jan. 20 in view of the assortment of surgical wounds. The suprapubic drain was removed on Jan. 18 and a self-retaining catheter inserted after sounding the urethra. On Feb. 2 the suprapubic wound appeared dry and the catheter was removed. The patient, however, had some difficulty in micturition, and urine soon began to leak suprapubically. The catheter was reinserted, and drainage was continued until Feb. 14, when the catheter was removed and the patient could urinate freely. On this date he was transferred to a urologist in Sudbury, Dr. M. L. Mader, who reported scarring at the vesical neck and did a transurethral resection.

Follow-up.—The patient made an uneventful recovery and is now in excellent health and able to walk ten miles daily without difficulty.

I wish to thank my partner, Dr. K. C. Soper, whose skill in anæsthesia made possible the successful outcome.

Reviews of Books

The Health of the Community

C. FRASER BROCKINGTON, M.A., M.D. Camb., D.P.H., barrister-at-Law, professor of social and preventive medicine, University of Manchester. London: J. & A. Churchill. 1954. Pp. 400. 32*s*.

THE factual content of this book is not so very different from that of other books of like title and subject, yet it is bright with new approach. The pieces of paper one puts into a kaleidoscope are only pieces of paper, but they become changed to patterns. Professor Brockington composes his pattern finely and has the power of capturing in few words a meaning, a doubt, an explanation, or a reassurance. Admittedly there are a few slips here and there—one in the author's words on child minding, and another in the section dealing with housing and standards of overcrowding. But this is not a work of reference, nor another primer of public health. Read as a whole or in part, it provides plenty of material for serious discussion and readers will argue, for example, over Professor Brockington's forthright claim that the future medical officer of health should coördinate all community health and welfare services. (Some of them may also argue over his horrifying statement that "Mary, Queen of Scots, does not seem very beautiful now by her pictures; she may have been thought a beauty . . . because of the fact that she had never been disfigured by smallpox.") The book is comprehensive, dealing historically and critically with the functions of the medical officer of health and nearly every aspect of his work.

Synopsis of Children's Diseases

JOHN RENDLE-SHORT, M.A., M.B. Camb., M.R.C.P., D.C.H., senior registrar, department of child health, Welsh National School of Medicine. Bristol: John Wright. 1954. Pp. 620. 32*s*. 6*d*.

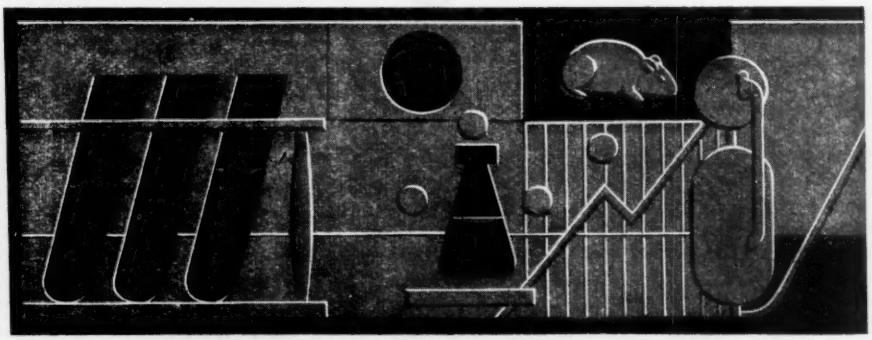
THE "Synopsis" series have a reputation for authority combined with brevity. This youngest member of the series, appropriately enough, deals with children's diseases, and it lives up to the standard of its predecessors. The staccato style, reminiscent of Mr. Jingle, does not make for easy reading; but then the book is not intended to be read in the normal manner but to be used for rapid revision and easy reference. As nothing of importance has been omitted, it will be helpful to undergraduates to have most of the diseases described as common, rare, or very rare. (Two major triumphs of preventive medicine are well demonstrated by the classification of rickets and diphtheria as very uncommon diseases.) The text is much more up to date than are most textbooks by the time that they reach publication. Such comparative newcomers as idiopathic pulmonary hæmosiderosis, hyaline membrane disease, and idiopathic hypercalcæmia are given brief but suitable descriptions.

The first section, dealing with normal growth and development and with infant feeding, lays particular stress on breast-feeding, and there is an excellent section on the newborn infant, with a sensible note on the psychological aspects of prematurity (which may affect the relation between the mother and child). Each main section has an introductory note on normal variations of infancy and childhood, and on special methods of investigation and examination. The tables of differential diagnosis of such symptoms and signs as jaundice, muscle wasting, stridor, and hæmatemesis are useful, and the section on the treatment of dehydration is particularly good. At the end of the book there is a list of the dosage of some common drugs for various age-periods from the newborn infant up to the age of 9 years. A surprising omission is the absence of any reference to the use of isoniazid in the treatment of tuberculosis—no doubt an oversight.

This is a work that should be deservedly popular, not only with examination candidates but also with doctors in practice.

Handatlas der Cystoskopie und Urethrocystoskopie (3rd ed. Leipzig: Thieme. 1953. Pp. 110. DM. 50).—This book consists mainly of paintings; and the late Prof. O. Kneise and Dr. M. Stolze, the authors, both experienced urologists, were themselves the artists. The first edition was published as long ago as 1907. There are 124 paintings, all in colour, arranged in seven sections depicting various types of bladder lesion, each section preceded by a brief discussion of the disease to be illustrated and the part played by cystoscopy in its diagnosis and treatment. There are some rather more general articles on the cystoscope and its use at the beginning of the book. The quality of the pictures is on the whole very good, though it does vary: thus the only nine pictures of urethrocystoscopic findings are poor. A still picture in one plane of one cystoscopic field is necessarily a fragmentary and artificial representation of the living bladder disorder, no matter how excellent the painting. This atlas cannot escape this limitation, but it provides interest, pleasure, and some instruction.

The Silent Shore (London: Hodder & Stoughton. 1954. Pp. 384. 12*s*. 6*d*.).—In this book by Mr. Denis B. Wylie, a strong-minded woman doctor, having delivered a school-friend of twins, a boy and a girl, takes an interest in the future history of the babies and the rest of the family, and extracts from her diary fill in the gaps in the narrative. Mr. Wylie's ebullience leads him to offer his readers a plot with too many incidents, lively conversations with too many jokes, and discussions on too many social problems. But his humanity ensures that none of these are trivial, and his hero's interest in the problems of the aged is an important part of the book. The book is pleasant reading, though perhaps not for strong-minded women doctors.



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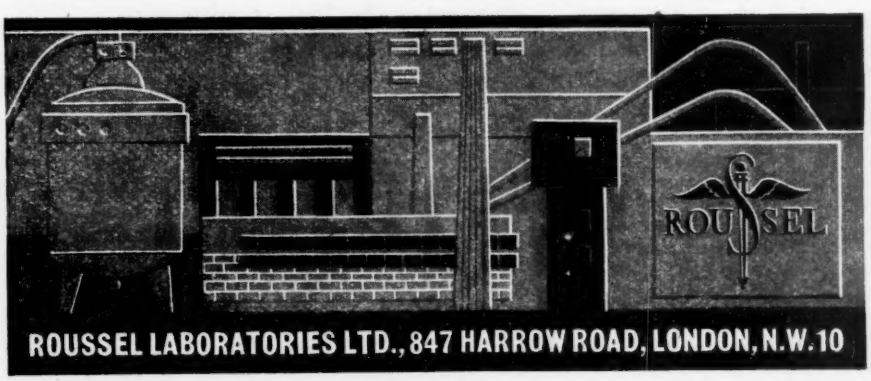

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LONDON: SATURDAY, APRIL 24, 1954

Pernicious Anæmia—a General Disease

PERNICIOUS anæmia is a misleading title. The disease is no longer "pernicious," since it can be successfully treated and controlled; and anæmia is only the most prominent of its manifestations. The curious megaloblastic change in the erythroblasts is not the only abnormality in the bone-marrow cells. The granulocytes also are affected; the leucopenia and the presence of multilobed polymorphs were known to the earliest investigators, and bone-marrow studies have shown significant gigantism among the metamyelocytes—the nucleus is unusually large and occupies more of the cell than normally. Another recognised complication of pernicious anæmia is a low platelet-count, sometimes with serious hæmorrhage. This again is now known to be paralleled by abnormalities in the platelet-producing cells of the bone-marrow—the megakaryocytes. EPSTEIN [1] has studied the megakaryocytes in bone-marrow biopsies of patients with pernicious anæmia in relapse, and in some found giant megakaryocytes with excessive nuclear segmentation. KISSMEYER-NIELSEN [2] thought that the megakaryocytes might not be producing platelets, and such platelets as could be found were large and coarse; but the number of megakaryocytes was normal. All these changes in the granulocytes and in the megakaryocytes are reversed when vitamin B_{12}, or any active treatment, is given.

The pathological changes in the nervous system that accompany pernicious anæmia have been known for over half a century. At one time it was suggested that these were due to a different deficiency from that responsible for the blood changes. Thus Sir ARTHUR HURST postulated the presence of a factor, "neuropoietin" (to contrast with hæmopoietin, the gastric intrinsic factor), that was necessary for the proper nutrition of cells in the spinal cord: the clinical syndrome of subacute combined degeneration of the spinal-cord tracts was the clinical expression of deficiency of this factor—a deficiency that might develop independently of hæmopoietin deficiency, thus accounting for the non-anæmic cases of the syndrome. But today it is recognised that vitamin B_{12}, a single substance which effectively corrects the anæmia, will also bring about certain arrest and some remission of the neurological changes; and it seems clear that the changes in the nerve-cells are part of the pernicious-anæmia syndrome. SAMSON and his co-workers [3] have investigated the changes in cerebral function associated with clinical pernicious anæmia and noted a significant diminution in awareness, accompanied by electro-encephalographic abnormalities. These changes, too, are completely relieved by treatment with vitamin B_{12} (such improvement precedes changes in the blood-count), and this they attribute to the effect of vitamin B_{12} on cerebral metabolism.

1. Epstein, R. D. *Amer. J. Path.* 1949, **25**, 239.
2. Kissmeyer-Nielsen, F. *Acta med. scand.* 1951, **141**, 125.
3. Samson, D. C., Swisher, S. N., Christian, R. M., Engel, G. L. *Arch. intern. Med.* 1952, **90**, 4.

The well-known glossitis of pernicious anæmia is also apparently a symptom of metabolic disturbance, this time in the epithelial tissues. It too can be controlled by vitamin B_{12}; but the action may not always be direct, since BROWN,[4] in Glasgow, showed that other single members of the B-vitamin complex, such as pantothenic acid or nicotinic acid, were effective by themselves.

GRAHAM and RHEAULT [5] now report changes in epithelial cells in patients with pernicious anæmia. In their laboratory cytological examination of gastric contents has revealed two types of cell. The majority are squamous epithelial cells from the upper respiratory tract and the œsophagus, most of which have been swallowed; they come from the superficial layer of the squamous epithelium. The other cells, which are fewer, are columnar epithelial cells from the gastric epithelium itself. In patients with untreated pernicious anæmia both these types show characteristic abnormalities. The squamous cells are considerably larger than usual; they sometimes have multiple nuclei as a result of abnormal mitosis; and the nuclear pattern, instead of being regular, is irregular with odd clumping of the chromatin. The gastric columnar cells are also larger than normal; and their nuclei show distinct increase of chromatin, which is irregularly distributed. When the patient is treated with vitamin B_{12} these abnormal cell changes become less pronounced, and in full clinical remission they cannot be detected at all. No such abnormalities were found in patients with comparable hæmoglobin levels due to iron-deficiency anæmia or acute blood-loss; so anæmia alone is not the cause. Nor do GRAHAM and RHEAULT think that the absence of free hydrochloric acid in the stomach is responsible. Once again lack of vitamin B_{12} seems to be the reason. It is noteworthy that in pernicious anæmia the cellular abnormalities—excessive size and distorted arrangement of chromatin in the nucleus—are similar in the epithelial and the hæmopoietic cells. What other cells, it may be asked, are likewise affected, and do the neurological changes follow cellular changes in the central nervous system? The mode of action of vitamin B_{12} is not yet clear, but VILTER and co-workers [6] and others have suggested that it is one of the essential components of the enzyme system concerned with the formation of nucleic acids. The blood-forming tissues are most severely affected because throughout life there is in them such a rapid turnover of cells. Both THORELL [7] and J. N. DAVIDSON and co-workers [8] have found that in pernicious anæmia erythroblasts tend to accumulate desoxyribonucleic acid in the nucleus, and ribonucleic acid in the cytoplasm, beyond the normal levels. The effect of vitamin B_{12} on the growth of animals [9] supports the view that it plays an important part in general cellular maintenance and multiplication. These nucleic-acid changes are engaging the attention of many investigators. Meanwhile it becomes clearer that megaloblastic anæmias are, as MALLARMÉ [10] puts it, cytological dystrophies;

4. Brown, A. *Brit. med. J.* 1949, **1**, 704.
5. Graham, R. M., Rheault, M. H. *J. Lab. clin. Med.* 1954, **43**, 235.
6. Vilter, R. W., Horrigan, D., Mueller, J. F., Jarrold, T., Vilter, C. F., Hawkins, V., Seaman, A. *Blood*, 1950, **5**, 695.
7. Thorell, B. *Acta med. scand.* 1947, suppl. 200, p. 52.
8. Davidson, J. N., Leslie, I., White, J. C. *Lancet*, 1951, **i**, 1287.
9. Zucker, T. F., Zucker, L. M. *Vitam. & Horm.* 1950, **8**, 1.
10. Mallarmé, J. *Blood*, 1948, **3**, 103.

in pernicious anæmia absence of vitamin B_{12} seems to be the cause, while in the megaloblastic anæmias of steatorrhœa and pregnancy folic-acid deficiency seems to be responsible.

All this new evidence makes it difficult to maintain the original idea that pernicious anæmia was due to a reversion of erythropoiesis to an embryonic form that produced red cells which could not stand up to the wear and tear of the adult circulation. It seems more likely that pernicious anæmia is a generalised disease of cell formation, and that the effect of lack of vitamin B_{12} on cell size and nuclear pattern becomes manifest in erythroblasts after the pro-erythroblast stage, and in granulocytes after the myelocyte stage. It is fortunate that so simple a treatment as the exhibition of vitamin B_{12} rectifies the multiple changes in this generalised disease.

Ureterocolic Anastomosis

DISSATISFACTION with the results of ureterocolic anastomosis has led to the development of new techniques. The pioneer methods of COFFEY [1] and STILES,[2] by which the ureter is led through the wall of the colon without direct anastomosis between the mucosæ of colon and ureter, have become less popular owing to their tendency to cause a stricture; this, though it may prevent reflux of gas or fæces up the ureter, interferes with drainage of the kidney, and hydronephrosis is very likely to develop. The direct techniques of NESBIT [3] and CORDONNIER [4] have the opposite disadvantage of often allowing reflux, and thus increasing the risk of renal infection. LEADBETTER [5] has sought to combine the advantages of both methods by a direct mucosa-to-mucosa anastomosis, with a valvular arrangement fashioned by burying the lower end of the ureter in a tunnel formed by the wall of the colon. PYRAH [6] reports that with this operation his own early results have been satisfactory.

Hardly any other abdominal operation gives rise to complications more commonly or in greater variety. Among the 1673 operations analysed by JACOBS and STIRLING [7] the immediate-morbidity rate was over 40%. Partly, no doubt, this rate is so high because the operation is usually done for severe genito-urinary disease, very often in elderly patients; but even in young patients in good general condition complications are common. JACOBS and STIRLING find that these number no fewer than fifty-nine. Of the "non-specific" complications in the large series that they review, ileus developed in 114 (6·7%) cases; and they suggest that excessive preoperative preparation of the bowel may have helped to precipitate this disorder. Burst abdomen occurred in 41 (2·5%) cases; and probable factors here were abdominal distension due to ileus, or simple gaseous distension in a weakened patient. Intestinal obstruction may result from adhesions or from strangulation of a loop of bowel between the ureter and the posterior abdominal wall. Fistulæ (urinary or fæcal, or combined) occurred in 9% of cases, and renal complications (including infection, uræmia, and urinary calculi) in 5%. The most important late complication is electrolyte imbalance.[8] As regards the clinical picture of this disturbance, nothing has been added to the description by FERRIS and ODEL [9]; and, despite much investigation, unanimity has not been reached on its cause. Most workers, including KEKWICK et al.,[10] LAPIDES,[11] and CREEVY,[12] believe that impaired renal function is the most important factor, but ROSENBERG [13] states: "the primary factor in the production of hyperchloræmic acidosis following uretero-sigmoidostomy is, in most cases, reabsorption of urinary constituents, primarily anions, from the large bowel." The experimental work of PARSONS and his colleagues [14 15] at Leeds and of ANNIS and ALEXANDER [16] has clearly shown that differential absorption of electrolytes takes place, chloride being absorbed in excess of sodium. PYRAH suggests that in cases of electrolyte imbalance with severe clinical symptoms the sequence of events is probably as follows: differential absorption of chlorides from the colon; renal infection leading to interference with the acid-base regulating mechanism of the kidney; excessive loss of base from the kidney and acidosis; progressive dehydration; nausea and vomiting leading to increased dehydration.

The treatment of electrolyte imbalance should be started in the immediate postoperative period. Continuous rectal drainage by an indwelling catheter should be maintained for seven days to prevent any rise in pressure at the site of the anastomosis, and to diminish the total amount of urine in the colon. Fluid balance must be carefully maintained, and the administration of electrolytes limited to the body's requirements. Sodium chloride must be given sparingly because of the differential absorption of chloride, and any sodium deficit must be met by giving sodium lactate as well as sodium chloride so that the final ratio of sodium to chloride is 1·4 to 1. When oral feeding is started a mixture containing 4 g. each of sodium and potassium bicarbonate is given every twenty-four hours. Fluid intake should be as great as is compatible with urinary output, to prevent renal infection; and any infection should be vigorously treated with a broad-spectrum antibiotic. PYRAH decides on the later treatment of electrolyte imbalance by the severity of the symptoms:

1. Patients who have no symptoms should be instructed to restrict the amount of sodium chloride in their diet, to take sodium bicarbonate 4 g. daily, and to micturate fairly often.
2. Patients with mild symptoms may be quickly relieved by reducing their sodium chloride intake and giving sodium bicarbonate 2–3 g. eight-hourly until the acidosis has been corrected.
3. Patients with severe symptoms, such as dehydration and nausea, should be treated in hospital under close laboratory control. The complex electrolyte disturbances require individual correction, but with rational treatment even apparently hopeless cases can be revived.

The many disadvantages of the operation have led to a search for alternative measures, and several

1. Coffey, R. C. *J. Amer. med. Ass.* 1911, **56**, 397.
2. Stiles, H. J. *Surg. Gynec. Obstet.* 1911, **12**, 127.
3. Nesbit, R. M. *Univ. Hosp. Bull. Mich.* 1948, **14**, 45.
4. Cordonnier, J. J. *J. Urol.* 1950, **63**, 276.
5. Leadbetter, W. F. *Ibid.* 1951, **65**, 818.
6. Pyrah, L. N. *Ann. R. Coll. Surg. Engl.* 1954, **14**, 169.
7. Jacobs, A., Stirling, W. B. *Brit. J. Urol.* 1952, **24**, 259.
8. *Lancet*, 1952, i, 453.
9. Ferris, D. O., Odel, H. M. *J. Amer. med. Ass.* 1950, **142**, 634.
10. Kekwick, A., Paulley, J. W., Riches, E. W., Semple, R. *Brit. J. Urol.* 1951, **23**, 112.
11. Lapides, J. *Surg. Gynec. Obstet.* 1951, **93**, 691.
12. Creevy, C. D. *J. Urol.* 1953, **70**, 196.
13. Rosenberg, M. L. *Ibid*, p. 569.
14. Parsons, F. M., Pyrah, L. N., Powell, F. J. N., Reed, J. W., Spiers, F. W. *Brit. J. Urol.* 1952, **24**, 317.
15. Parsons, F. M., Powell, F. J. N., Pyrah, L. N. *Lancet*, 1952, ii, 599.
16. Annis, D., Alexander, M. K. *Ibid*, p. 603.

methods of constructing an artificial bladder have been devised.[17] One of the minor disadvantages of an artificial bladder is the production of considerable quantities of mucus, which may lead to blocking of a catheter. GODFREY [18] has found that preliminary irradiation of the ascending colon greatly reduces the secretion of mucus, and he suggests that it also diminishes the reabsorption of electrolytes. PYRAH describes a method of avoiding a ureterocolic anastomosis which may prove useful in some cases of contracted bladder. An isolated loop of lower ileum is prepared, one end is closed, and the other end is anastomosed to the solitary ureter. A wide side-to-side anastomosis is then made between the bladder and the ileal loop. This considerably increases the bladder storage capacity and relieves frequency of micturition.

By the development of such techniques, the conditions for which there is no alternative to ureterocolic anastomosis may be reduced in number. In PYRAH's [6] words:

> "The operation of ureterocolic anastomosis is not a procedure like appendicectomy for gangrenous appendicitis or cholecystectomy for gallstones, which finally removes from the patient a diseased organ which may be threatening life; it is rather a procedure which, by producing a fundamental change in the excretory arrangements of the body, often confers great benefits on the patient, but also carries risks of renal infection and derangement of the blood electrolytes that are sometimes inimical to health and occasionally dangerous to life. It is reasonable, therefore, that . . . attempts should be made to relieve the pathological process for which it is performed by some alternative procedure."

The A.R.D. Virus?

SOMEWHERE in the no-man's-land between epidemic influenza and the common cold lies a group of febrile upper respiratory infections which are not normally epidemic. In 1938 STUART-HARRIS, ANDREWES, and SMITH [19] described a syndrome which was more insidious in onset, and was more usually accompanied by sore throat and cough, than infection with influenza-A virus. This syndrome was named "febrile catarrh" to indicate the catarrhal manifestations—obstructed nose, hoarse voice, signs of tonsillitis or pharyngitis, and exudation of mucous or mucopurulent secretion. Individual cases could not be separated from influenzal infections, but the two conditions were thought to be distinguishable in the mass. The U.S. Army Commission on Acute Respiratory Diseases [20] described a similar condition which they called "undifferentiated acute respiratory disease," or A.R.D.; and they also spoke of cases of atypical pneumonia and exudative pharyngitis, although it was not known whether these three conditions represented different clinical manifestations of the same ætiological agent. A.R.D. was particularly common among new entrants to the army—unlike influenza, which attacked new recruits and old stagers indiscriminately. The commission [21] also investigated the ætiology of this disease in volunteers. In 12 out of 14 volunteers, a filtrate of nasopharyngeal secretions from a typical case produced a mildly febrile respiratory illness five to six days after inoculation, and tests of immunity distinguished this infection from the common cold. These findings suggested that A.R.D., which is probably the same condition as "febrile catarrh," is a distinct entity with a rather longer incubation period than has been described for influenza and the common cold and is probably caused by a filtrable virus. The extent of A.R.D. in the general population is unknown, and this would be extremely difficult to assess without a laboratory test for the ætiological agent.

It is good news, therefore, that attempts to isolate an ætiological agent from an outbreak of A.R.D. at Fort Lennox Wood, Missouri, by inoculating tissue-cultures of HeLa cells (from a uterine carcinoma), have resulted in the recovery of a new virus. HILLEMAN and WERNER [22] examined 29 throat washings and recovered 5 cytopathogenic agents, presumably viruses, from 3 cases diagnosed as primary atypical pneumonia and 2 diagnosed as A.R.D. Apart from its cytopathogenic action, the distinguishing features of the virus are not yet known; but serological tests by neutralisation of the virus's cytopathogenic action, and complement-fixation tests, have yielded important results. Each of 7 cases of primary atypical pneumonia and 6 of 7 cases of A.R.D. from this outbreak showed a fourfold or greater rise in antibody to the new virus. No rise in antibody to this virus was found in sera from patients with influenza A or B, psittacosis, ornithosis, or Q fever, or in 3 cases diagnosed as primary atypical pneumonia in which there were significant increases in cold or streptococcus MG agglutinins. The results suggest that the new virus may be a cause of some cases of A.R.D. or primary atypical pneumonia. HILLEMAN and WERNER mention that the agent they describe has proved to be immunologically related to a virus recovered earlier by ROWE et al.[23] from cultures of adenoid tissue. These workers noted that during long in-vitro cultivation of adenoids obtained at operation on young children many of the cells showed a characteristic rounding, progressing to complete destruction of the epithelium. Transfer of these cultures to HeLa cells resulted in identical changes in the recipient cells; and the causative agent, which was filtrable, has been called the "adenoid-degenerating" or A.D. agent. It is important to find out whether the A.R.D. and A.D. agents are the same or are simply members of the same family. Possibly the upper respiratory passages harbour a group of related viruses (cf. the pneumococci) of which some members are latent and harmless commensals while others can cause A.R.D. or primary atypical pneumonia. Alternatively this virus may be of no ætiological significance in A.R.D. but may multiply when the ground has been prepared by the A.R.D. virus. This does not seem very likely, but the recovery of Coxsackie and poliomyelitis viruses from the same patients should warn us against jumping too readily to conclusions. It will be of great interest to see what the new virus and the A.D. virus do to the long-suffering volunteer who is prepared to risk febrile catarrh and possibly degeneration of his adenoids.

17. *Ibid*, 1953, i, 1186.
18. Godfrey, G. *Aust. N.Z. J. Surg.* 1954, **23**, 161.
19. Stuart-Harris, C. H., Andrewes, C. H., Smith, W. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1938, no. 228.
20. U.S. Army Commission on Acute Respiratory Diseases. *Amer. J. publ. Hlth*, 1944, **34**, 347.
21. U.S. Army Commission on Acute Respiratory Diseases. *J. clin. Invest.* 1947, **26**, 957.
22. Hilleman, M. R., Werner, J. H. *Proc. Soc. exp. Biol., N.Y.* 1954, **85**, 183.
23. Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., Ward, T. G. *Ibid*, 1953, **84**, 570.

Annotations

PROSPECTS IN THE CIVIL SERVICE

THE long deadlock over the salaries of Civil Service doctors has at last been broken, on the terms which we publish on p. 878. The commencing salary of a medical officer (at the age of 35) is to be £1500, and the maximum salary in this basic grade will be £2100, which is a substantial advance on the present scale of £1250–1725. The Treasury would like the new scale to be permanent, but the committee which represents Civil Service doctors does not accept it as adequate and will be putting its arguments before the Royal Commission on the Civil Service, of which Sir Raymond Priestley is chairman. Increases of £100 and £50 are also made in the salaries of senior medical officers and principal medical officers; but these are regarded by all parties as no more than a token, and the Royal Commission will be asked to consider what the appropriate salaries should be. In the medical Civil Service as elsewhere, outstanding merit should bring commensurate reward, and responsibility should have pecuniary recognition.

The new scales operate retrospectively from Jan. 1, 1952; and this is only proper, for their negotiation has a long and not a happy history. As far back as 1948 the Institution of Professional Civil Servants asked that the recommendations of the two medical Spens reports should be applied to Civil Service medical officers; to which the Treasury replied that Spens was not applicable. In conjunction with the Ministry of Health Medical Staff Association and the B.M.A., the institution then formed a Civil Service Medical Officers' Joint Committee, which in August, 1949, presented a salary claim based on the two reports. After rejecting this in February, 1950, the Chancellor of the Exchequer said that he would appoint a committee to consider the remuneration, structure, and organisation of the medical Civil Service; and in the autumn of 1951 the Government accepted the recommendations of the Howitt Committee which had been charged with this task. But neither the constitution nor the conclusions of the Howitt Committee were acceptable to the profession,[1] which did not feel that the problem had had the full and judicial examination it deserved. The British Medical Association declined to accept further advertisements for Civil Service medical appointments; and, in associating ourselves with a request for fuller and more objective consideration of the subject, we said that "in the (perhaps unlikely) event of advertisements being submitted, we intend to add to each of them an indication to possible applicants that conditions of remuneration and promotion for doctors in the Civil Service have not yet been satisfactorily settled."[2] With this rupture the difficulty of obtaining good medical officers became even greater.

In the further study of recruitment for the medical Civil Service which the Royal Commission will no doubt undertake, we hope that emphasis will be placed as much on prospects of promotion as on the level of remuneration in the basic grade. In some departments there are few senior posts and the prospects for an able man are poor—a situation recognised by the Howitt Committee when it suggested that a doctor with exceptional qualifications, bearing responsibilities heavier than those usually falling on officers of his grade, should (with Treasury sanction) be allowed personal promotion. Commenting on this, we said: "Our impression is that, unless this loophole is greatly enlarged, the service, on the proposed salary scales, is unlikely to secure first-rate specialist members in the future."[1] This remains true; yet it seems to be nobody's business to see that the loophole is made into something more useful.

1. *Lancet*, 1951, ii, 921.
2. *Ibid*, 1952, ii, 119.

PENICILLIN BY MOUTH

SINCE penicillin first became available in quantity many attempts have been made to find a reliable method of administering it by mouth, and many vehicles have been suggested for this purpose. The relative instability of penicillin in acid solution, and the low blood levels following its oral administration, led to the belief that acid in the stomach destroyed much of each dose. Preparations in alkaline or buffered solutions, or in enteric-coated capsules designed to dissolve after passage through the stomach, were therefore investigated in an attempt to prevent such destruction; but no method has given constant and reproducible results. In all the earlier investigations high serum concentrations were attained in some patients, while in others penicillin could not be detected in the blood, whatever buffers or capsules were used as the vehicles.

The explanation now generally accepted for this unpredictability is that the power to absorb the drug from the intestine varies widely between different people, and that destruction by gastric acid is of minor importance. The capacity to absorb penicillin can be assessed only by trial and error, which is usually impracticable; so clearly progress in this field can come only from the development of compounds that are uniformly and reliably absorbed by all patients. This property has been claimed for N : N′-dibenzylethylenediamine penicillin (benzathine penicillin), though the inconsistencies in the reported trials suggest that the requirements may not be completely satisfied.[1–4] Elsewhere in this issue we include two further reports on benzathine penicillin. Dr. Fairbrother and Dr. Daber have compared its value with that of potassium penicillin, mainly in adults; while Dr. Beasley and Dr. MacPherson have investigated the absorption of benzathine penicillin in children of various weights.

The outstanding conclusion to be drawn from Fairbrother and Daber's report is that the absorption of benzathine penicillin from the intestine is no more constant or reliable than that of the potassium salt. In fact the results suggest that potassium penicillin is possibly the more satisfactory compound. In only 1 of 35 patients to whom 600,000 units of potassium penicillin was given by mouth was no penicillin detected in the blood four to six hours later. In a further 8 patients the blood level at this time was only 0·03 unit per ml.; this is often regarded as the minimum therapeutic level, though, as Fairbrother and Daber point out, it may often be clinically ineffective. Among 59 adult patients, four to six hours after administration of 600,000 units of benzathine penicillin no penicillin was detectable in 11 instances, and only 0·03 unit per ml. was found in another 11. Thus blood levels exceeding 0·03 unit per ml. four to six hours after the dose were observed in 74% of patients receiving potassium penicillin and in 62% of patients receiving benzathine penicillin. The absorption of benzathine penicillin by 31 children seemed more satisfactory in that no instances were encountered in which penicillin was undetectable in the blood. The interpretation of these findings is difficult, however, since the ages and weights of the children are not specified, and no comparable study of potassium penicillin is reported.

The importance of weight in relation to dosage is clearly seen from the report by Dr. Beasley and Dr. MacPherson, who have determined for children of various sizes the doses of benzathine penicillin required to give 0·03 unit per ml. in the blood after four, six, and eight

1. Bayne, G. M., Gylfe, J., Carfagno, S., Boger, W. P. *Amer. J. med. Sci.* 1953, **225**, 190.
2. Cathie, I. A. B., MacFarlane, J. C. W. *Brit. med. J.* 1953, **i**, 805.
3. Welch, H., Randall, W. A., Hendricks, F. D. *Antibiot. Chemoth.* 1953, **3**, 1053.
4. Wright, S. S., Purcell, E. M., Kass, E. H., Finland, M. *J. Lab. clin. Med.* 1953, **42**, 417.

hours. No parallel study of other types of penicillin was made; but the large size of the doses required to ensure absorption, even in quite small children, suggests that benzathine penicillin cannot be greatly superior to the potassium salt.

These reports focus attention once more on the practicability of oral administration of penicillin. Repeated injections are always inconvenient in general practice, and in children they should be avoided if possible. Possibly, too, the incidence of sensitivity reactions might be diminished by oral administration. Nevertheless, the attainment of an effective concentration at the site of the infection has priority over these considerations; and, as Fairbrother and Daber point out, a single daily injection of 400,000 units of procaine penicillin costs less and gives more uniform results than 600,000 units of penicillin by mouth every six hours. For severe infections the administration of penicillin by mouth in any form seems clearly to be unjustified unless the antibiotic is also given parenterally in the early stages. In all other cases, before resorting to administration by mouth on the ground of convenience very careful consideration should be given to such factors as the sensitivity of the infecting organism, the danger of encouraging resistant organisms by inadequate dosage, and the severity of the infection.

CORTICOTROPHIN AND ADRENAL HORMONE IN URINE

MUCH of our knowledge of metabolism is derived from the analysis of urine. Although this gives only indirect information about what is going on inside the body there are advantages in using such material, which the patient can provide without hardship and which is in some ways more pure than the body-fluids themselves.

Rubin et al.[1] have recently demonstrated corticotrophin-like activity in the urine of some normal persons by injecting the urine into hypophysectomised rats and measuring the fall in the ascorbic acid content of the rats' adrenals. The urine of one patient with Cushing's syndrome possibly had a greater effect than normal urine. On the other hand Rubin et al. did not find any increase in the activity of urine from children with rheumatic fever who were receiving corticotrophin. The significance of these findings is not yet clear.

The effect of corticotrophin on the excretion of adrenocortical hormone is a fruitful field for research. The adrenal steroids in urine have been measured chemically and by biological assay, and certain derivatives without biological activity can be demonstrated after hydrolysis with glucuronidase. Cope and Hurlock[2] have applied the method of paper partition chromatography to the separation of cortical steroids in human urine. They have distinguished hydrocortisone (compound F) and cortisone, and two important steroid metabolites—tetrahydro-compound F and tetrahydrocortisone. The tetrahydro-compounds do not possess hormonal activity and may represent breakdown products of hydrocortisone and cortisone. The excretion-rates of all four compounds increased with administration of corticotrophin and after a major operation. Tetrahydrocortisone was usually present in greater amounts than tetrahydro-compound F, but the excretion of hydrocortisone often exceeded that of cortisone. All the compounds were much reduced in patients with hypopituitarism. When these patients were given cortisone, the excretion of cortisone and also of hydrocortisone and of the two tetrahydro-compounds increased. This suggests that cortisone is converted to hydrocortisone in the body, and that the adrenals do not necessarily play a part in the conversion. Evidence is accumulating that hydrocortisone may be the active "sugar hormone" of the adrenal cortex; and this would explain, for instance, why hydrocortisone is more effective than cortisone when injected into rheumatic joints.[3]

1. Rubin, B. L., Dorfman, R. I., Dorfman, A. *J. clin. Endocrin.* 1954, **14**, 154.
2. Cope, C. L., Hurlock, B. *Clin. Sci.* 1954, **13**, 69.

MICROGYRIA

MICROGYRIA is a manifestation of severe dysplasia of the cerebral or cerebellar cortex, in which the convolutions are not only reduced in depth but also seemingly increased in number. It has to be distinguished from ulegyria, which is a thinning of the gyri due to scarring acquired after birth and often as a result of it; and to make the distinction clearer it is sometimes called polymicrogyria. It may be seen in the cerebrum or cerebellum of mental defectives and even in those of more normal mentality, while its association with other congenital anomalies, both in the brain and elsewhere, is well known: Norman[4] noted the condition in 8 out of 45 cases of cerebral palsy. The convolutions are often rather wide, and their surface is finely wrinkled—an appearance that has been likened to a chestnut kernel. The abnormality, however, may be confined to the deeper convolutions, as Obersteiner showed in 1902, and may not be visible on the surface. A brain with microgyria involving many convolutions may be unduly small,[5] but this association with micrencephaly is by no means invariable. The cortical architectonics vary considerably, but not infrequently they conform to a pattern in which there are four instead of the usual six layers of cells, with a conspicuous fibre lamina dividing them up into two main layers. The junction between the normal and the pathological may be abrupt.

Bielschowsky[6] explained the anomaly as a failure of the neuroblasts migrating from the matrix to reach the periphery. One would thus expect the condition to be bilateral, but it was unilateral in 2 of the 6 cases, unassociated with porencephaly, reported by Norman.[4] Ulegyria, too, may be bilateral, usually in the neighbourhood of the sagittal sinus; on the other hand, it tends to affect small areas of the cortex, to be sharply defined, and to be especially severe in the depths of sulci.[7] Hallervorden[8] thought that this characteristic deep-seated position was the result of severe congestion during birth. Clearly, therefore, it may be difficult to distinguish ulegyria from polymicrogyria. Doubtless many cases of ulegyria have, in the past, been regarded as examples of true microgyria, and this confusion is likely to continue in the future. Referring to brains which show structural anomalies at an early age, Norman[4] remarks: "In the absence of clear-cut signs of malformation pathological criteria alone are usually insufficient to allow one to determine with confidence whether the damage to the brain has occurred during the later stage of pregnancy, during birth, or in early infancy"; and Malamud[9] has arrived at the same conclusion. It would seem, therefore, that ulegyria tends to be labelled microgyria (or polymicrogyria) more often than the converse.

Of 3 cases of microgyria reported by Crome,[10] instrumental deliveries are mentioned in 2 but in the third no clear history was available. One child, who died at the age of 12, had been retarded from birth and had been epileptic from the age of 18 months; a dissimilar twin was normal. The other 2 children survived until the ages of $7\frac{1}{2}$ and almost 2. In all 3 brains the microgyria was associated with micrencephaly

3. Dixon, A. St. J., Bywaters, E. G. L. *Ibid*, 1953, **12**, 15. See also *Lancet*, Feb. 27, 1954, p. 448.
4. Norman, R. M. *Proc. R. Soc. Med.* 1953, **46**, 627.
5. Greenfield, J. G., Wolfsohn, J. M. *Arch. Neurol. Psychiat.* 1935, **33**, 1296.
6. Bielschowsky, M. *J. Psychol. Neurol., Lpz.* 1915, **22**, 1 *Ibid*, 1923, **30**, 29.
7. Norman, R. M. *Arch. Dis. Childh.* 1944, **19**, 111.
8. Hallervorden, J. *Z. ges. Neurol. Psychiat.* 1939, **167**, 527.
9. Malamud, N. International Congress of Neuropathology, September, 1952; see *Lancet*, 1952, ii, 635.
10. Crome, L. *J. Path. Bact.* 1952, **64**, 479.

and compensatory hydrocephalus, and in 2 of them there was paraventricular calcification, so that radiologically some confusion might arise in distinguishing this disease from tuberous sclerosis or even toxoplasmosis. Crome noted that the microgyria was usually more extensive than it first seemed, for when the sulci were examined closely cryptomicrogyria was often found. His third case was associated with arhinencephaly and porencephaly, but the microgyria was restricted in each hemisphere to an area around the Sylvian fissure. He concluded that there must have been defective development of the brain, and the symmetrical distribution supported this view; but the covering membrane over the porencephalic cyst showed histological evidence of the destruction of existing brain tissue, so the defective development might itself have been the result of a destructive lesion during early development. This deduction is in keeping with the view of Cohen and Neumann[11] who believe that vascular occlusion early in fœtal life will cause maldevelopment or even agenesis.

When microgyria is associated with porencephaly the question arises whether the second condition is strictly a complication of the first—the result, for instance, of a secondary vascular softening—or whether the disturbance of the fœtal brain which gives rise to porencephaly also causes microgyria in the adjoining cortex. Yakovlev and Wadsworth,[12] in their extensive studies, divide the porencephalies into the schizencephalies—"a manifest disorder of tectogenesis"—and the encephaloclastic porencephalies, but they do not seem to exclude the possibility of mixed forms. In one of their cases lesions of three different ages were found; one of them probably dated from birth, and the other two were earlier, thus illustrating, they suggest, a sequence of superimposed events brought about by a chain of largely obscure causes "in which the circulatory disturbances and the destructive encephalomalacic lesions represent an incidental and fortuitous factor." If the cause of porencephaly is complex, the same can be expected of microgyria, which it so often accompanies. Provided, however, that there is no question of delay in the migration of neuroblasts to the cortex, the disturbance of the fœtal brain that produces true microgyria would be expected during the fourth or fifth month—the time when migration normally takes place.

Hydrocephalus, it seems, may also be looked for in association with microgyria. Crome described it in each of his 3 cases, but Norman found it in only 2 out of 6 cases, and in both of these the cortical defect was bilateral. Of particular interest in this respect is a case described by Hallervorden.[13] A married woman in the fifth month of pregnancy made an unsuccessful attempt to commit suicide with coal gas. The baby was born at the expected time, but failed to develop normally and later suffered from athetosis. The head was retracted and there was severe lordosis of the lumbar spine. The child died at the age of 1. True microgyria was present in parts of both frontal lobes; and microscopically there was widespread loss of nerve-cells in the third layer of the cerebral cortex. Both putamina showed cavitation and scarring, and so did the lateral thalamic nuclei on the right side. The brain thus showed what was apparently a prenatal malformation dating from about the fifth month of fœtal life, and in addition there was evidence of gross softening of the basal ganglia and other vascular lesions. The possible part played by anoxia in microgyria is referred to by Meyer and Cook,[14] who found gliosis in the white matter of mental defectives, including those with microgyria; but they pointed out that defective tissue oxygenation is often merely a final common pathway of ætiologically distinct disease processes.

There is clearly much to learn about the cause of microgyria. A history of trauma at and after birth in defectives is hard to elicit, and it is known that serious birth injury may take place in apparently normal labour[15]; but reliable evidence of intra-uterine events likely to cause encephaloclasis or otherwise disturb the development of the nervous system is impossible to obtain.

11. Cohen, R., Neumann, M. A. *J. Neuropath.* 1946, **5**, 257.
12. Yakovlev, P. I., Wadsworth, R. G. *Ibid*, p. 116.
13. Hallervorden, J. *Allg. Z. Psychiat.* 1949, **124**, 289.
14. Meyer, A., Cook, I. C. *J. ment. Sci.* 1937, **83**, 258.
15. Brouwer, B. *Proc. R. Soc. Med.* 1949, **42**, 603.
16. Isbister, C. *Arch. Dis. Childh.* 1954, **29**, 66.
17. Waller, H. Clinical Studies in Lactation. London, 1937; p. 37.

THE DRAUGHT REFLEX

THOSE in charge of the management of lactation need to understand the draught reflex. The mother finds description elusive, and exact recording sometimes takes part in the conditioned reflexes which set it off. The mere act of thinking of the reflex may bring it into action before its proper time. Yet the doctor or midwife depends largely on subjective accounts since there is little objective evidence by which to detect vagaries of the reflex that may be producing feeding difficulties.

Dr. Isbister[16] has sought to analyse the usual behaviour of the reflex and some of its variations by questioning many mothers as well as making observations on herself. She confirms Waller's[17] finding that most primiparæ feel the reflex for the first time only after about three weeks, whereas multiparæ may feel it even before delivery; and she confirms, too, that nearly all successful feeders experience it. Many of the mothers questioned had noted that sometimes the draught was delayed and seemed to last less long than usual—particularly when they had been suffering embarrassment, fatigue, or worry. Anger roused just before feeding delayed the draught by two minutes. Dr. Isbister suggests that too vigorous action of the reflex may in some instances be responsible for wind, colic, vomiting, and frequent stools in the baby; and, to avoid this difficulty, she recommends evoking the reflex before the feed by expressing a little milk. Like Waller, she believes that gastro-intestinal symptoms in the infant may be due to gulping large quantities of milk; but perhaps they may sometimes be the outcome of maternal fear transmitted humorally in the milk. The mother's fear of suffocating her baby may be great, and assurances that the baby can manage the situation if given his head are often as effective as any other remedy for the baby's disturbances.

HALF-WAY HOUSE

ON March 31 an important experiment was set in train at Liverpool when Sir Henry Cohen and the Bishop of Liverpool opened a hostel administered by the Liverpool Personal Service Society. The regional hospital board has contracted for the use of 18 of the beds by patients transferred from hospital who are not yet fit to return home. The remaining 20 beds are available to the local health authority for patients who are aged and frail but who do not require medical and nursing care. Experience with this hostel may answer some of the questions concerning borderline cases that are neither fully the responsibility of the hospital service nor fit enough for the type of hostel provided by the local health authority under the National Assistance Act. The progress of this experiment will be keenly watched not only by the administrators of these two branches but also by general practitioners, who are in a good position to see the ill effects of the hiatus that the new hostel is designed to fill.

ON April 12 Sir RUSSELL BRAIN was re-elected president of the Royal College of Physicians of London for the ensuing year.

Reconstruction

A DIAGNOSTIC CENTRE

THE Nuffield Diagnostic Centre at Corby in Northamptonshire is being opened on April 23 by Lord Nuffield. The centre has been sponsored by the Nuffield Provincial Hospitals Trust and the Oxford Regional Hospital Board, and it has been designed as part of a plan to meet the medical needs of the rapidly growing town of Corby.

The Plan for Corby

In 1934 Corby was a village with a population of about 1500. Messrs. Stewarts & Lloyds then opened the first part of the steelworks there; the industry has been expanding ever since, and Corby has grown with it. In 1950 a development corporation was established, under the terms of the New Towns Act, to help the urban district council in their work of development. The steel industry is to be further enlarged, and light industries will, it is hoped, increase too. The aim is a town of 40,000; and one of the corporation's main tasks was the provision of a town centre, and this is now well under way. Close to the town centre there is a large area of woodland, and it is here that the diagnostic centre has been built; and an adjoining site has been reserved for the hospital and clinic buildings that may be added later.

In 1949 the Nuffield Provincial Hospitals Trust examined the medical needs and opportunities of Corby, and the result was the formation of a committee which was asked to draw up a plan to meet these needs. The committee included representatives of the Trust, the Oxford Regional Hospital Board, the Northamptonshire County Council, the Northamptonshire Executive Council, the Corby Urban District Council, and Stewarts & Lloyds. It was clear that no new hospital could be built for a long time, yet something had to be done to meet the difficulties of the general practitioners, who had no convenient means of investigation or consultation for their patients. As things were, they had to refer them to Kettering (8 miles away) or Northampton (25 miles); and this meant much inconvenience and loss of time for the people of Corby, and much extra work for the nearest hospital, at Kettering. So the Trust proposed to all concerned that there should be set up

> "a diagnostic centre, which will include examination and treatment rooms to be used by the general practitioners, and also by the hospital service as a consultant outpatient department; chest clinic, and X-ray and physiotherapy departments; and a dental suite."

And this centre forms the first stage in the plan for Corby. (For the time being, at the suggestion of the Ministry of Health, the dental suite has been omitted.) Later, a maternity unit will be added by the regional board, and there may also be a unit of general-practitioner beds. The existing local-authority clinics in the area are at present sufficient, but when extra clinics are needed they will be built beside the diagnostic centre.

The hopes are that this scheme will not only enable the Corby doctors to provide a better service for their patients but also lessen the burden on Kettering General Hospital and other hospitals in the district.

The Design

The centre has been designed by Mr. R. Llewelyn Davies, A.R.I.B.A., the director and architect of the Trust's Investigation into the Functions and Design of Hospitals; and he has had the help of Messrs. Gotch, Saunders, & Surridge, architects, of Kettering. One purpose of the experiment was to show that the essentials for a diagnostic centre of this kind could be provided at a reasonable cost. The contract price for the building was rather less than £34,400, and the cost of furnishing and equipping it was about £13,000; and this is certainly modest by health-centre standards. The contract price works out at a few pence over £3 10s. per sq. ft. of floor space; the permitted expenditure on private houses is usually around £2 per sq. ft., but the architect clearly has a lot more to do in each square foot in a diagnostic centre than in an ordinary house. And Mr. Llewelyn Davies and his colleagues have done very well in building an efficient and pleasant building for such a sum.

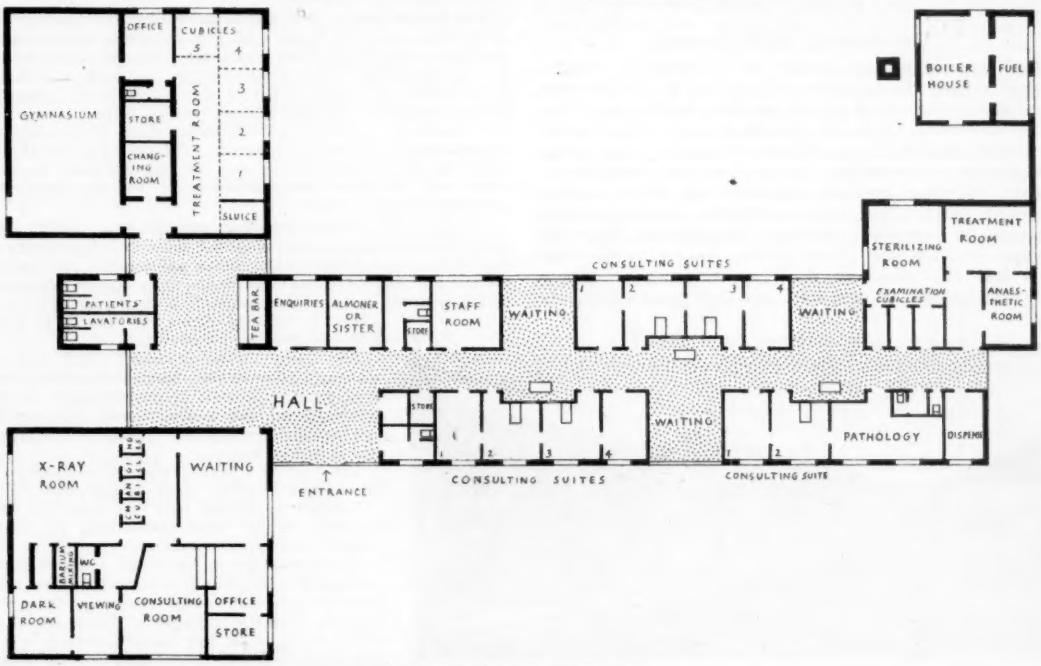


Fig. 1—Plan of the diagnostic centre.

The three parts of the building—the consulting and treatment wing, the physiotherapy department, and the combined chest clinic and X-ray department—are neatly arranged around a central entrance hall and reception desk (fig. 1). Waiting-spaces, rather than waiting-rooms, have been fitted into the design, and there are splendid wall-high windows to light them (fig. 2). The consulting-rooms, which will be used by both G.P.s and consultants, have examination rooms alongside, and one of the consulting-rooms is equipped for the ophthalmologist. They all have 'Anglepoise' lamps and viewing-boxes fitted to the walls.

The compact and well-provided pathological laboratory is down the same corridor; and further on there are the treatment rooms. Three small cubicles are equipped for dealing with patients who have dressings to be changed, and the small treatment room and anæsthetics room will enable the doctors to undertake many more minor operations than they could hope to do in their surgeries.

The physiotherapy block includes a remarkably roomy gymnasium (fig. 3) with plenty of things to keep the patients hard at it. The department can take on anything that a bigger hospital one can do; the only limitation is its size and the physiotherapist's one pair of hands. It remains to be seen how great will be the call on his services and those of the specialist in physical medicine: they could be the busiest people in the place.

The X-ray department is superbly equipped; the tilting table will be the envy of visiting radiologists. Again, it is difficult to say straight away how much work there will be for the radiographer, but there is no doubt that it will be well done. If the planners have been lavish anywhere in the centre, it is here. No serious casualties will be brought to the centre for X-ray examination, because there are at present no beds to receive them or resident medical staff to attend them. But this may come later.

To keep the bills down, the architects have had to be pretty strict in their choice of materials. They have used plenty of glass to give a cheerful exterior—always difficult to achieve in a single-storey building. And they have chosen a pale sandy-coloured brick of pleasant texture which does not, as the yellowy bricks often do, emphasise the virtues of the reds. Internal walls in corridors and waiting-spaces have been left unplastered; and on these walls bold colour washes have been used to distinguish one part of the building from another.

The Working of the Centre

The centre does not qualify to be called a "health centre" under the definition of the N.H.S. Act of 1946, for it does not include all the facilities laid down in the Act. Moreover, it is not provided by a local health authority, and the G.P.s will not work in it as a group. The doctors will continue to use their own surgeries in Corby; but when they see a patient who needs a more thorough examination and investigation than they have the time or means to undertake immediately, they will arrange to see him later at the centre, where the G.P.s will rent some of the consulting-rooms. There they will be able to deal with the case more effectively

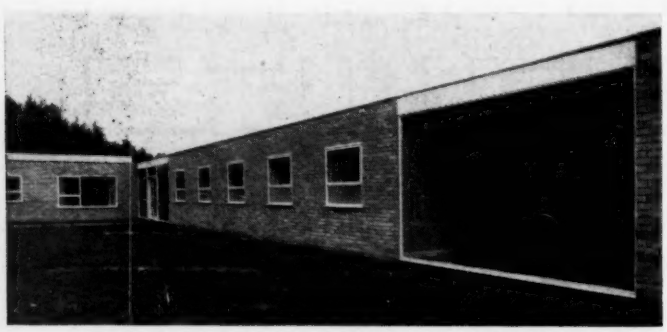


Fig. 2—A view of the centre showing one of the large windows.

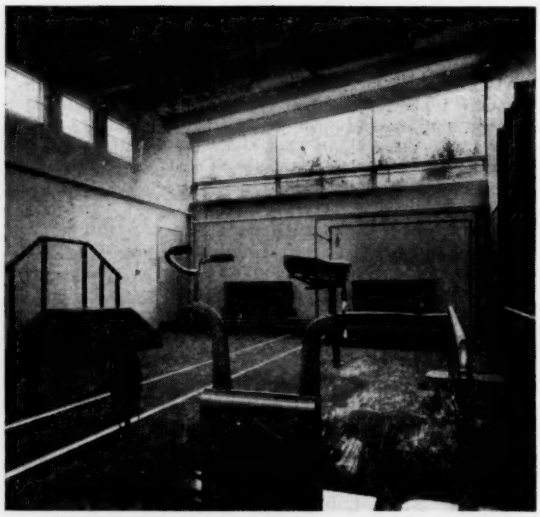


Fig. 3—The gymnasium in the physiotherapy department.

than they can usually do during busy surgery hours. The X-ray department and pathological laboratory will be to hand, and they will be able to consult colleagues who are using the centre in the same way or arrange for an opinion from one of the consultants who visit the centre for specialist clinics. If he is able to be there when the consultant sees his patient, the G.P. (and the consultant) will have the added advantage of direct contact; and, indeed, it is hoped that direct consultation between G.P. and consultant will be one of the most useful features of the new centre. To encourage this side of things, arrangements have been made for G.P.s to become clinical assistants to the consultants visiting the centre.

The Authorities Concerned

The *Oxford Regional Board* is providing and staffing the chest clinic and the X-ray and physiotherapy departments, and the board will pay a fee for the use of the consulting-rooms by its consultants and specialists. At the start, the clinics to be held at the centre will be: medical, surgical, obstetric, and gynæcological, pædiatric, chest diseases, physical medicine, psychiatric, ear, nose, and throat, radiological, dermatological, ophthalmological, and orthopædic. The pathological laboratory, the X-ray department, and the physiotherapy department will be under the direction of the corresponding consultant at Kettering.

At the end of the five-year experimental period, the *Northamptonshire County Council* will have the opportunity of buying the Trust's share in the centre. Meanwhile, the council is contributing £100 a year towards the maintenance expenses; and it will pay for any accommodation that may be needed when its existing clinics are unable to cope with the growing population.

The *Corby Urban District Council* has no statutory place in the affairs of the centre, but it is paying the rent of two cottages for the resident staff and is also meeting the cost of the laying-down and the upkeep of the lawns and flower-beds.

The *Corby Development Corporation* is providing a house for a physiotherapist.

Stewarts & Lloyds will contribute to the running costs of the centre during the early years of the experiment.

The capital for building and equipping the consulting and minor-treatment rooms and the pathological laboratory has come from the *Nuffield Provincial Hospitals Trust*, which is also helping with the initial running costs. The *Nuffield Health and Social Services Fund* has transacted much of the business for the

Trust, and the ultimate control and coördination of the centre has been vested in the Fund. The Fund has sold part of the site to the regional board, and it is keeping another 5 acres ready for the board to build the maternity and G.P. units.

Administration and Staff

The day-to-day running of the centre is in the hands of a local management committee, appointed by the Fund. The Kettering and District Hospital Management Committee is responsible to the regional board for its part of the centre, but by a happy arrangement the house committee chosen to look after this part of the centre is man-for-man the same as that appointed by the Fund for the Trust's side of things. The group secretary of the Kettering committee is administrator in charge of the centre. The staff, at any rate for the time being, is a sister, staff nurse, assistant nurse, physiotherapist, radiographer, laboratory technician, almoner, receptionist, and 2 typists. Stewarts & Lloyds have also offered the help of their social relations officer.

The Value of the Experiment

Whatever the differences between a "diagnostic centre" and a "health centre," it is certain that progress at Corby will be judged partly in relation to the health-centre experiments that are under way in various parts of the country. In the matter of cost, the Corby centre is dearer than the centres at Harlow,[1] Bristol,[2] and Nottingham [3] (where no attempt was made to provide special methods of investigation), and inexpensive by the standards of Woodberry Down [4] and Sighthill.[5] But, in counting the cost, the important point is that something was urgently needed at Corby: a hospital was out of the question, and the Nuffield centre was a likely answer. The particular interest of the experiment lies in the possibility that it will turn out to be an answer applicable in other districts where populations are large and hospitals small or far away.

To enable them to keep a close watch on developments, the Trust organised, in the late summer of 1953, a survey of the domestic, social, and economic difficulties that arose from the lack of a hospital and outpatient department in Corby. A year or two from now the same details will be re-examined, and it will then be possible to make a preliminary judgment of what the centre has done for the people of Corby. It will also be interesting to know what weight of work it has taken off the back of Kettering Hospital and other hospitals. There will be less doubt of the advantages to the general practitioners, who will have a splendid surgery-from-home, as well as an opportunity to draw added help from the consultant service and, indeed, to take part in it.

Medicine and the Law

Spinal Anæsthesia

THE decision in Woolley and Roe *v.* Ministry of Health and others,[6] which we announced briefly last week, may not only mystify the layman but also leave the lawyers in some uncertainty.

The two plaintiffs, after undergoing minor operations in the Chesterfield and North Derbyshire Royal Hospital, became permanently paralysed from the waist downwards. 'Nupercaine,' supplied in glass ampoules, had been administered as a spinal anæsthetic, and at the trial Mr. Justice McNair found that injuries were caused by phenol percolating through invisible cracks into the ampoules from the solution in which they had been immersed. The layman may be surprised that patients could be refused compensation when so grave and apparently inexcusable an injury could happen to them in hospital. The lawyers may feel puzzled because, although the trial judge decided that the facts did not speak for themselves (thereby establishing a prima-facie case of negligence), Lord Justice Denning now holds the contrary view. The hospital authorities in his opinion were responsible for the whole of the staff; he did not think that the hospital authorities and the anæsthetist could both avoid an explanation by each throwing the responsibility on the other. Lord Justice Somervell was prepared to regard the visiting anæsthetist as part of the permanent staff of the hospital, like the orthopædic surgeon in Cassidy *v.* Ministry of Health in the case which he helped to decide in 1951. The visiting anæsthetist, he said, was (like the orthopædic surgeon) a qualified skilled man, controlling as such his own methods. "The position of surgeons and others under the National Health Act will have to be decided when it arises, the position of hospitals under that Act may or may not be different from that of voluntary or municipal hospitals." We must wait, it appears, for further expensive litigation in order to find out how the law stands.

In the recent appeals the trial judge had found that phenol could find its way into an ampoule of nupercaine, stored in a phenol solution, through cracks undiscoverable by ordinary visual or tactile examination. The anæsthetist had not appreciated this risk, but, judged by the standard of medical knowledge to be imputed to competent anæsthetists in the year 1947, the anæsthetist was not negligent in failing to appreciate the risk; a fortiori the theatre staff were not negligent. The Court of Appeal accepted and adopted this view; and so, however sympathetic everyone must feel to the plaintiffs, the claim for damages failed. In Lord Justice Denning's words which we have already quoted, "we must not condemn as negligence that which is only a misadventure."

Injury during Removal of Plaster

In Sunderland County Court,[7] a 65-year-old man was recently awarded £60 damages for a 14-inch cut inflicted by the shears when a male staff-nurse removed a plaster cast from his leg. The man had to have 28 stitches in his leg and was kept in hospital another three weeks. In his evidence, the senior orthopædic surgeon at the hospital described the staff-nurse, who had won a merit award since the accident, as an extremely conscientious worker, and he thought he had been unfortunate in dealing with a patient who did not say he was being cut; there must have been some diminution of sensation. Lord Uvedale, resident surgeon at Manor House Hospital, to which the patient was subsequently admitted, said he had never before seen such an injury from plaster removal.

The judge said it was not a case in which the hospital had to be punished for injuring the patient, but a matter of compensation. He had come to the conclusion that the patient had not felt the pain normally and that the sensitivity of the skin was diminished because the plaster had been on for 6 months. The staff-nurse had not carried out the removal with his customary skill.

Death from Anti-tetanus Serum

A verdict of misadventure was returned at an inquest at Southwark [8] on a girl machinist who had died soon after a small test injection of anti-tetanus serum. She had run a needle into a finger at work and it became infected. When she attended St. Olave's Hospital, Rotherhithe, the surgeon ordered her to have anti-tetanus serum, and in preparation for this a test dose was injected by a nurse into the girl's leg. She became unconscious, had convulsions, and died despite artificial respiration and injection of "heart stimulants." Dr. F. E. Camps, the Home Office pathologist, said that a section cut through the injection site showed that the needle had entered a small vein so that the serum was injected straight into the blood-stream.

1. Taylor, S. *Lancet*, 1952, i, 253.
2. Wofinden, R. C., Parry, R. H. *Ibid*, p. 1297.
3. *Ibid*, 1952, ii, 931.
4. *Ibid*, p. 772.
5. *Ibid*, 1953, i, 1039.
6. *Times*, April 9, 1954.
7. *Yorkshire Post*, April 2, 1954.
8. *South London Press*. April 6.

Special Articles

DIFFERENTIAL DIAGNOSIS
AN APPARATUS TO ASSIST THE LOGICAL FACULTIES

F. A. NASH
M.R.C.S.

MEDICAL DIRECTOR, SOUTH WEST LONDON MASS X-RAY SERVICE

THERE are at least three ways in which one learns medicine: from first-hand experience at the bedside, from spoken and written accounts by others of individual cases they have seen, and from written generalised accounts of many similar illnesses grouped into what we call diseases. The student has two tasks: he must learn the symptoms and signs of all the important diseases, and he may also try to learn all the diseases that cause each particular symptom. The former task is usually better done than the latter. To help him to learn about diseases he has the descriptions given in the "straight" textbooks, while to help him to learn (or look up) the diseases that cause particular symptoms there are books which give the differential diagnosis of separate main symptoms.

THE MECHANISM OF DIAGNOSIS

What happens in the doctor's mind when he is faced with a patient? This will depend on his experience, on his book knowledge, and on his mental endowment; but the diagnosis will be made in one or all of the following ways.

(1) The patient's story and the results of physical examination may bring into action the subconscious process of immediate recognition of the disease. The diagnosis here is made in the same way as we "diagnose" the identity of our friends—i.e., without conscious formulation of reasons but with a high degree of confidence and accuracy. This capacity for recognition diagnosis is the invaluable possession of the doctor who has had much experience in practice and has profited by it.

(2) The doctor may recall descriptions from books or from memories of practice of several diseases that might fit the patient's story. This process of recalling to consciousness the diseases that enter the differential diagnosis is not usually a logical effort but relies on the storehouse of the memory to "throw up" several likenesses to the present patient. That it is far from being the infallible result of an act of volition is suggested by the experience that more things are missed through not being thought of, and so not looked for, than through not being known. The doctor will try to hold in his mind's eye the descriptions of the diseases he has "thought" suitable for consideration in his differential diagnosis, and to see which best fits the patient's case as he has elicited it. In no case will his patient have *all* the described symptoms of any of the textbook diseases, because they are collective descriptions. The individual case presents usually but a tattered fragment of the full-blown composite picture of the disease described in the textbook.

This task of assessing the significance of all the patient's symptoms together and relating them to a disease is extremely difficult. Theoretically the doctor could go through the descriptions of diseases in his straight textbook—i.e., review it from cover to cover to find the description that most nearly fits his patient. But in practice one cannot re-read a textbook for each patient.

(3) The doctor may take a main or significant symptom or sign, and, using it as an intellectual straw to cling to, or start from, in a sea of memories and observations, he may review the diseases that could cause it. He may do this for several of the patient's symptoms in turn, perhaps using a book on the differential diagnosis of main symptoms to help him. If he uses a book like French's *Index* he will find his fingers in different pages on which are given lists of causes of those of his patient's symptoms he tries to look up. To find the disease names that occur every time under each separate symptom as shown in different parts of the book may be far from easy, even with pencil and paper to hand. To hold the several lists of possible causes of each of the patient's different symptoms and signs in mind at once and logically to select those causes that best explain—i.e., are common to—the largest number of his symptoms is beyond the capacity of most minds.

However differential diagnosis is approached, our literary tools will not enable us to recall without fail all the diseases that could be the causes of the symptoms and signs, taken together, of each particular patient. The inadequacy of these tools is inherent in the structure of the *page* as the unit holder of data, owing to its rigidity—i.e., its inability to present the relevant data in the order or pattern that may be required. What is needed is a device which will answer the question "What are the possible causes of the group of symptoms and signs I have elicited from my patient?" Theoretically a giant table containing hundreds of vertical columns of symptoms and signs and hundreds of horizontal rows of diseases would suffice, but such a table would be as big as the wall of a room and far too unwieldy for practical use.

The reason why no such device has been found is that the only commonly used fact-holder has been the book or a card, both of which hold the facts as symbols on a page. The continuous use of the page for thousands of years makes it unnecessary to speak of its advantages for recording. Yet we may conceive that the book, and particularly its unit the page or card, may not be the ultimate form of record. Though some of the defects of the bound book are obviated by the loose-leaf ledger or card system, even cards have the limitations inherent in their structure. In narrative records side-by-side comparison of groups of data is impossible, and the table on a single page or folding sheet is a sign that a vague want is felt for devices to display any required relationships. Unfortunately if one makes a table big enough to include as much data as would occupy a whole book of narrative type, the thing becomes utterly unmanageable. For any particular problem we have in mind, the table is cluttered with irrelevant data that obscure the data and their relationships that we are trying to trace.

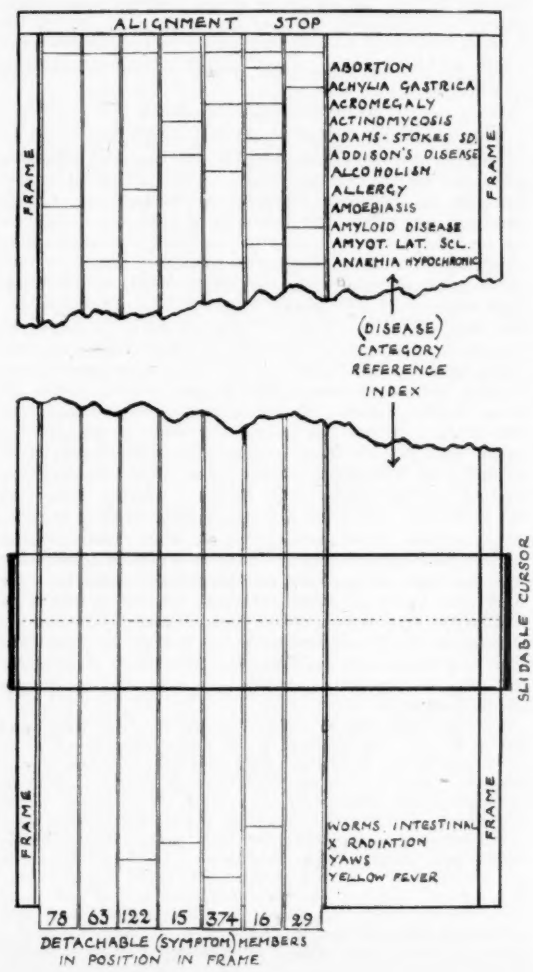
Apparatus

The solution offered here is a mechanical table with hundreds of removable columns which allow the manipulation at will of any chosen groups of qualitative data. It is a supplement to books and a mechanical aid to certain types of logical thinking.

The device consists of a frame to one side of which is fixed a category reference index. In the index the categories (in this instance diseases) are listed one beneath the other (in the prototype in alphabetical order). A space is provided in the frame into which fit a number (8 in the prototype) of detachable members of strip form which are inserted with their longitudinal axes parallel to the category reference index. Each detachable member carries a reference to the symptom or other attribute concerned—e.g., hæmoptysis—and on its exposed surface is graduated (or written on) at right angles to its longitudinal axis in all those places which (when the member is in position in the frame) align with a category (disease) in the index in which the symptom the strip represents is known to occur. There may be hundreds of detachable strip members which are conveniently stored in a separate index ready for use when wanted. They can each represent any chosen single attributes—e.g., symptoms, signs, age-incidence, and sex-incidence of diseases.

The prototype contains about 300 diseases. This list when typed is about 4 ft. 3 in. long. By photographic reduction this was made into a scale about 2 ft. 3 in. long. The scale can be reduced still more, so that the list of 300 diseases is only 18 in. long. The symptom members are made of obeche wood (*Triplochiton scleroxylon*). In the diagram the symptom members are numbered, but in practice it is preferable for the name of the symptom to be printed on each one.

To obtain classification of a number of attributes to a particular category or categories, the appropriate members are taken out of the store and inserted one beside the other in the frame. It will then be seen that each symptom has its own spectrum or pattern of causation. It will be also seen that in some places two or more of the spectral lines lie adjacently against the same disease, with the result that on the apparatus it looks as if a single straight horizontal line has been drawn across several or all of the symptom units opposite that disease. Our patient's disease must be one of these diseases that would account for all or most of his symptoms. These can be seen literally at a glance. One can also see at once which disease would explain some of his symptoms but not others. Roughly, the diseases with the longest horizontal composite lines against them will be those we should consider as possible diagnoses in our particular patient whose symptoms we earlier fitted into the machine. Such a preliminary review of the range of diagnostic possibilities and probabilities could precede and to some extent guide the physical examination and investigations. However, if desired, sign strips or units can be made on the same principles as the symptom strips and the whole case can be put into the machine for analysis and consideration. Although in the prototype the spectral lines have been used, it would be possible to use adjectives, figures, or other symbols instead—e.g., on the cough unit bar, instead of a simple linear spectrum, one could have adjectives such as brassy, gander, and stridulous, in the appropriate places—i.e., opposite diseases to which they are applicable. It is intriguing to find how many causes the apparatus can suggest for one or two of a patient's symptoms or signs, and how, as more and more of the patient's symptoms are inserted, the range of possibilities rapidly narrows.



Discussion

What does the apparatus described do? It tells us what diseases could account for any particular group of symptoms we care to put into the machine. Its programme of symptoms and signs is potentially as great as the repertoire we decide to give it. A book will not arrange data in the way required for the solution of particular individual problems, and for this reason the man who merely knows the books by heart cannot apply the knowledge he has to particular problems. His associational ability to extract and associate information from different parts of the book is of a low order.

Limitations of Apparatus

The machine can only suggest which diseases a particular patient may have, and so give the doctor some jumping-off points in thought from which he can go on to consider the most likely diagnosis or what further observations he needs to help clarify the issue. The apparatus will also indicate some points against certain diagnoses that may have spontaneously occurred to the observer. It is not a substitute for any of the human faculties needed in the difficult art of differential diagnosis. All it can do is to assist, and so perhaps improve on, the workings of the unaided ordinary mind in certain parts only of the process of diagnosis. Any diagnostic aid, whether book, list, or other device, can never be the sort where one puts in a penny and out comes the diagnosis, because no apparatus will ever be able to take a proper history, examine the patient intelligently, and possess clinical judgment.

Logically the apparatus can be said to have the purpose of stating the inclusion or exclusion of classes in reference to one another, especially in demonstrating the relationships of overlapping classes. Thus, when we say "This patient has a cough" we could be considered logically to be saying "This patient is a member of the class of all coughers." The "class of all coughers" will be distributed among many groups of ill people who have the different diseases of which cough forms a part. Other classes of persons with other symptoms will overlap the class of all coughers in so far as they occur in the same diseases as cough. To put the matter more traditionally, the symptom strips represent grouped data about certain qualities, attributes, or characteristics of the diseases or other entities listed in the reference category index.

Summary

Books and card indexes have shortcomings inherent in their unit, which is the page. When we use them as fact-holders they impose on us rigidity in the arrangement of data.

A physical aid to thinking, which may be called the group fact manipulator or associator, is described.

The apparatus allows the free manipulation at will of prefabricated groups of data for the solution of classificatory problems in medicine and other subjects. If the symptoms of a particular patient are put into the device, it will indicate at a glance the range of differential diagnostic possibilities. It is a supplementary aid and in no way a substitute for books, knowledge, experience, or clinical judgment. Like any tool it can be misused; but time may give it a useful, though limited, place in teaching and practice.

REMPLOY

FROM A CORRESPONDENT

No other industrial concern has quite so curious a problem to solve as Remploy Ltd.; or is more exposed to political cross-fire. Cannon to right of them, cannon to left of them, fairly describes the situation. On the one hand are those who say that Remploy factories should be purely a social service for the severely disabled, giving them somewhere to work and to feel they are earning a living. On the other are those who think that the country cannot afford sentimental luxuries, that it is cheaper to support these men and women in idleness on public-assistance funds, and that anyhow with proper management Remploy factories could be made to pay their way.

If Remploy factories could in fact be made to pay their way, of course, most of their critics would be silenced. Most of them, however, run at a loss, anyhow on paper; and according to industrial experts they always will, though the degree of loss may be reduced in time. Partly because these severely disabled people tire easily, partly because they are more often away sick than healthy workers, and partly because it has not always been possible, so far, to keep them supplied with steady runs of work, they have not been able to achieve and maintain more than a third of the output of workers in ordinary industry. The overhead costs of running a factory, however, go on all the time, whether the employees are working fast, slowly, or not at all. That is the crude financial problem—though only one aspect of it. There are others, and there are many other sides to Remploy; so we should look more closely at what they are doing, what they have done already, and what they hope to do, before assessing even the financial loss or gain.

RAPID EXPANSION

Remploy Ltd. was formed in 1945, under the Disabled Persons (Employment) Act, 1944, as a public corporation financed by Treasury funds, to provide employment for people on section II of the Disabled Persons Register—that is, for people so severely disabled that they are unable to work under ordinary industrial conditions. It has thus no choice about the type of person it employs.

In the nine years since it was founded Remploy has opened 90 factories; indeed all 90 were in action within seven years of the start. It has been much criticised for forging ahead so fast, instead of proceeding more cautiously and learning by experience; but it had no choice. The pressure on it—from Ministries, local authorities, and the public—was so great that it was obliged to set up factories much faster than it wished, or thought advisable. Between March, 1949, and March, 1950, for instance, it set up 26 factories.

There are at present some 6000 people employed by Remploy. The number of disabled on section II of the register who were still unemployed in January, 1954, was 5592; so the factories have not yet absorbed all the available labour from their pool. Some of these disabled unemployed, however, are doubtless unemployable; some live too far from the factories; and some will not be fit for factory work, though they may be able to do work at home. Remploy has already begun to organise homework schemes on a small scale, and is so far employing 137 people in this way.

The disabilities of Remploy workers include those due to injuries and amputations, congenital malformations, arthritis, diseases of the digestive and genito-urinary systems, diseases of the heart, circulatory system, and lungs (including pulmonary tuberculosis), skin diseases, ear and eye defects, organic diseases of the nervous system (including epilepsy, disseminated sclerosis, and poliomyelitis), mental defect, neurosis and psychoneurosis, and many others.

The average age of the workers is high compared with that of workers in ordinary factories, for most of them have tried and failed to make a living in open industry, many have been unemployed for years before entering the service of Remploy, and some have never worked before.

An analysis made in November, 1952, showed that 64% of the men were over 40, and 42% were over 50; more than a quarter were over 55. The women were relatively younger—only 26% of them being over 40, and only 10% over 50; but only about 350 women are employed

On entry, most of the workers are quite unskilled in the trades Remploy has to offer them, and they have to be trained. Again, many of them have psychological difficulties associated with their disability, or with long unemployment. Moreover, idleness—as anyone who has been obliged to try it for any length of time well knows—corrupts the will to work. Again, when Remploy started, its workers were not entering long-established factories with a team spirit and a social life of their own; these things have had to be built up gradually. To begin from scratch, with employees who know nothing of each other, or of the work, is never an easy task; and the disabled, being as human as the rest of us, have among them old-soldier types who will do as little as they can for the money, and sea-lawyers who can air a minor grievance with a wealth of rhetoric. The number of such characters varies with the place in which the factory is set: some areas breed tougher types than others. Fortunately most of the workers in any of the factories are glad to find themselves in productive work again, and taking home a pay packet instead of collecting an allowance.

MATERIALS AND MARKETS

The problems in management which the workers present are at least equalled by the practical and industrial problems which Remploy has to solve. Thus it has to provide its factories where the disabled are chiefly grouped, not where the demands of industry could best be served. In some places it has been possible to take over Government premises, or to rent a factory; but quite often Remploy was obliged to build, and this has been expensive. The goods to be made have to be within the compass of the workers, not too tiring or heavy to handle, not exposing sick people to extra industrial risks (such as dust risks), and not likely to cause annoyance to any section of open industry by cutting across its lines of production. Remploy tries never to undercut the market price: its goods are sold at commercial rates, and sell on their merits. Materials have to be available in sufficient quantity; and steady markets are needed so that there shall be no "waiting time" in the factories. Morale is a delicate plant of slow growth, easily struck down, and the man who comes to the factory and does nothing for days on end may reasonably suppose that he is living on the nation's charity. He may also feel that when the next job comes along he had better spin it out. Both ideas hinder production.

With so many answers to find it is small wonder that Remploy has not always found the right ones. Its greatest difficulty has been in securing long runs and continuity of production.

Knitwear has proved a great success in these ways, and one at least of the group of six factories doing this kind of work has shown a profit. Cardboard-box making is also relatively successful, though here delays in getting some kinds of appropriate material have proved troublesome. Light engineering, and electrical assembly work, have in these days permanently good markets; and the "preservation, identification, and packing" (P.I.P.) of other manufacturers' goods for transport or export also provides steady work. There is a limited demand for such things as school and hotel furniture and bedroom suites; and surgical footwear and appliances are slow and expensive to make (whoever makes them). Other trades offered by Remploy include mattress-

making, printing and bookbinding repairs, strapmaking, textile sewing, the making of equipment for the Forces, and brush-making.

WORKERS ON PRODUCTION

One difficulty in the London area is to find suitable factories. The following brief account of three of them gives some ideas of the degree to which Remploy has overcome its difficulties.

I

The first, set in an industrial estate in a busy London suburb, is in an old factory, rented for this purpose, and not fully suited to its task: the windows are not large enough and the lighting system—by modern standards—is poor; but it is roomy and warm. It employs about 90 men in making orthopædic footwear, callipers, tripod walking-sticks, crutches, 'Polythene' splints, and luggage straps. Their average age is 46. Their work was beautifully finished (this was true of all the work seen in Remploy factories), and in particular the orthopædic footwear they were making was much lighter and more supple than that usually inflicted on the lame: many disabled patients know from experience where the orthopædic boot pinches—or rather, how much it can weigh.

Great difficulty was experienced, at first, in getting the local hospitals to give this factory's work a trial. It was only when one hospital's supplier was snowed under with work that Remploy was given an order for a pair of shoes: the work was not only well done, but was done within a very few hours, and this hospital now always gives the factory a proportion of its orders for orthopædic footwear. The men in the orthopædic workshop were all cheerfully busy at the time of the visit, but some of those in the woodwork department were idle: orders had temporarily run out. It was evident that the men found this as unsatisfactory as the management—the difference in mood in the two workshops was noticeable.

II

The second factory, well to the east of London, in the dock area, takes about 110 men. No fewer than 18 of them are epileptics; and the medical officer of the factory—a general practitioner working part-time—remarked on the good effect of steady work on these patients. Many of them have lost job after job because of their fits. When they have had 3 or 4 fits on the factory premises without any attempt being made to get rid of them, they cheer up wonderfully, and as a rule their fit-rate falls considerably. This factory makes laminated furniture from wood veneers, turning out a great variety of pieces, from chairs and school furniture for the London County Council, to television tables. There are continuous markets for some of these goods (television tables seem to be a strong line at present). Others do not sell so freely, and some take long to make.

Much of the work requires a fair amount of active movement, or quite long periods of standing. Though none of the men questioned admitted to feeling tired, it seems likely that their output may have been slowed by fatigue. They have, however, a factory medical officer who is interested in methods of reducing fatigue, and ingenious in inventing devices for the purpose. They also have a good first-aid attendant, one of their own number who has been a bomb-disposal sergeant, whose concern for their well-being evidently gives them great confidence.

The men in this factory included some who were unstable, and at times inclined to violence. Remploy does not discharge workers because of troublesome behaviour except as a last resort, and after long months of trial and retrial; even then the discharge is made at the topmost level by the executive director. This ensures for the disabled the security they need; but it does not make any easier the task of management.

III

The third factory, in the suburb of a coastal city, employs only tuberculous disabled: Remploy has seven of these "special" factories scattered about the country. This one was built for its purpose, and while it is light, airy, and equipped with a good canteen (and a very good cook) it is short of storage space. It makes cardboard boxes, a commodity which cannot be compressed, and stacks of finished work stand about in every available corner, awaiting removal.

This factory, which will take 55, has 41 workers at present, 20 of them women. Most of the work is done sitting down, and it is neat skilled work, very suitable, it seems, for these people. Here again there is a good deal of machinery, but of course of a much lighter type, and more easily attended than that required in making furniture.

There was a cheerful pleasant atmosphere about the factory, where men and women were working together. They work hard and are keen on the job, but they tire towards the end of the day. Some attend the neighbouring hospital at intervals for pneumothorax refills or other treatment, and they are fatigued when they return. Most work full-time however; only 9 work half-time (four hours daily). The output here is better on the average than for many Remploy factories; and the manager hopes that as manual nimbleness improves, and as orders become continuous and steady, output will improve even more.

SOME FUTURE PROSPECTS

The managers of these three factories were of totally different types: what they had in common was an ability to get on with their workers, and a thorough knowledge of their own industries. They face at close quarters the problem which confronts Remploy as a whole: how to get each of their workers to contribute as much as he can without driving him to do more than he should. Remploy was established for the good of these disabled people, not to make a profit, so the managers probably err on the side of caution. One reasonable way of encouraging a man to do his best is to offer him a bonus on his output; and a bonus system has been introduced into one factory, making mattresses, with good success in stepping up production. But it would not do to introduce a bonus system in a factory which has much waiting time.

The first thing to ensure, then, is that Remploy makes goods for which there is a constant demand. This was pointed out by the Select Committee on Estimates [1] in 1952. The committee also made some useful suggestions on the organisation of sales on a trade basis instead of a geographical basis; but Remploy already had this in mind, and it has now been done, with advantage. Remploy also now has a managing director as well as an executive director and a financial director. These and various other changes have made it possible for Sir Robert Burrows,[2] the chairman, to note in his annual report a reduction of £62,613 on the previous year's loss.

Nevertheless, the loss for the year was high—nearly £2,380,400—and Remploy has plans for reducing it next year. Some of the factories are to be turned over to work which can command steadier markets, such as the assembling of electrical equipment, knitwear, and the making of elements for steam irons (which promise to be very popular). The cardboard-box factories can supply the containers for such small objects, and the P.I.P. factories can pack and dispatch them. With such steady lines it will probably be possible to introduce bonus systems into more factories, and so encourage production. Moreover, every year Remploy workers become more skilled in their trades, and newcomers are now entering factories with a good team and social spirit. Homework schemes, too, will be extended, and these should bring good returns because there are few overhead charges. A central sales showroom is to be opened at Cricklewood, and the export trade, which has just begun, will be developed. All these measures should help to bring down costs.

COSTS

Remploy workers get three-quarters of a normal full-time wage, even though their output is only a third of normal. This rate has been agreed with the trade unions. At present, as Sir Robert Burrows put it, the cost to each of us of employing these 6000-odd disabled people is 11½*d.* per head per year. It seems little enough looked at in this way; and there are some hidden advantages we get for our subscription which we all ought to take into account. Thus by March, 1953, Remploy had already returned some 1435 people to open industry: it had acted, in fact, as an unofficial reablement service. Again, though it would cost less, on paper, to pay these workers

1. Training, Rehabilitation, and Resettlement. London: H.M. Stationery Office, 1952.
2. Remploy Ltd., Annual Report 1952–1953.

from public-assistance funds, that would not allow for additional costs in sickness benefit likely to be needed by disabled people out of work, with nothing but their ills and failure to think about. The country, moreover, benefits by purchase-tax on Remploy goods sold, and by income-tax from the workers—figures which do not appear in the balance-sheet. Finally, some of the costs which do appear are merely figures on paper: thus, if a factory belongs to the Government, and Remploy pays rent for it, has money done more than circulate through a closed channel? Such rentals, however, help—on paper—to swell the figure for Remploy's trading loss.

Experts seem agreed there must be some financial loss on this project. Against this must be set its value, in mental and physical health and in self-respect, to the individual disabled person. We are willing to help these people at some cost to ourselves, and though we might do it a little more cheaply in other ways, the financial saving might not be worth the waste of spirit.

AMERICAN COLLEGE OF PHYSICIANS

FROM A CORRESPONDENT IN THE U.S.A.

As president of the Royal College of Physicians of London, Sir Russell Brain was the guest of honour at the 53rd annual meeting of the American College of Physicians, held in Chicago from April 5 to 9. He spoke on Cervical Spondylosis and on Problems of Cerebrovascular Disease, and he also lectured to the students and faculty of the University of Illinois College of Medicine. On less formal occasions he managed to astonish the few who still believe that "Britishers don't have a sense of humour."

The American College of Physicians was founded in 1915 by Dr. Kurt Stern and was patterned by him after the Royal College in London. Its fellows are selected from physicians in the United States, Alaska, Hawaii, Canada, Mexico, and the Caribbean Islands. The governing bodies consist of officers, regents, and governors. The officers and regents are an executive body and are chosen from former governors. Each governor represents the fellows of his State, province, or territory in North America, and, with governors from the United States Federal Services they number 67.

Election to fellowship in the American college usually comes after a three-year apprenticeship as an associate, and the fellowship is conferred each year by the president at the annual convocation.

Because the fellows are scattered over a continent and its islands, the headquarters in Philadelphia has never developed into a professional and social centre. To overcome the geographical problems, the American college holds small regional meetings and a large annual meeting in one of the important medical centres of North America. Here, each year, fellows, wives, and families congregate for a week of lectures, clinical and television demonstrations, panel discussions, and clinicopathological conferences. Besides these offerings and visits to local medical schools and hospitals, the main business of the college is transacted and a social programme is organised for the fellows and their guests.

The most important function of the college is the annual convocation. This year the processional of the officers, regents, governors, newly elected fellows, and distinguished guests was led by the president, Dr. LeRoy Sloan, professor of medicine at the University of Illinois. He conferred fellowships on 200 new fellows and masterships on four fellows. He presented the John Phillips memorial medal to Dr. Donald Van Slyke for his many contributions to clinical chemistry, and the James D. Bruce memorial medal to Dr. David Marine for his work on endemic goitre. He then conferred honorary fellowships on Prof. U.S. von Euler, of Stockholm, and on Sir Russell Brain. In conferring the latter Dr. Sloan spoke movingly of the close ties between the American and London colleges, and he indicated that these bonds were to be further strengthened. At the end of the ceremony, Sir Russell Brain asked for the floor, and presented a gift from the Royal College of Physicians. This was a replica of the caduceus presented in 1540 by John Caius and carried ever since by the presidents of the Royal College. This was, Sir Russell believed, the first time that a president of the Royal College of Physicians had ever carried out official duties in the United States, and he was delighted to be at the convocation and to deliver in person the following message:

"We, the President and Fellows of the Royal College of Physicians of London, meeting in Comitia on January 28th, 1954, send by the hand of our President greetings to the American College of Physicians. Our two Colleges are united by a common tradition in medicine and by the constant interchange of new knowledge. We welcome this opportunity for strengthening the ties of friendship which already exist between many physicians in our two countries, and we offer to our sister College every good wish for her continued prosperity."

This message and the gift of the caduceus were greeted with obvious pleasure by the members of the American college; and when the processional withdrew from the convocation hall we noticed that Dr. LeRoy Sloan was carrying the caduceus in his hand. It is to be hoped that future presidents will carry on the tradition he has started.

PAY OF CIVIL SERVICE DOCTORS

THE pay of three grades of medical officer in the Civil Service has now been revised, and the new scales are to operate retrospectively from Jan. 1, 1952. They are:

Grade	Age	Salary Scales (basic pay plus addition) Old scale	New scale
		£ s. d.	£
Basic grade	35	1331 5 0	1500
	36	1382 10 0	1575
	37	1433 15 0	1650
	38	1485 0 0	1725
	39	1536 5 0	1800
	40	1600 0 0	1900
		1675 0 0	2000
		1750 0 0	2100
		1825 0 0	
Senior medical officer		£1900 × 100 — £2100	2200
Principal medical officer		£2250	2300

The negotiations which have led to this conclusion have been carried out by the Civil Service Medical Officers Joint Committee, composed as follows:

Dr. A. J. OWSTON (chairman); Dr. E. A. GREGG, Dr. A. MACRAE, Dr. D. P. STEVENSON, and Dr. H. K. COWAN (British Medical Association); Dr. N. R. BEATTIE, Dr. A. F. ALFORD, and Dr. E. MARTIN (Ministry of Health Medical Staff Association); and Dr. A. I. G. MCLAUGHLIN, Dr. J. H. MURDOCH, Dr. A. B. WALKER, Mr. STANLEY MAYNE (secretary), and Mr. T. H. PROFITT (Institution of Professional Civil Servants). As from the beginning of this year, the Ministry of Health Staff Association has brought its membership within that of the Institution of Professional Civil Servants.

The new scales are provisional in that both the committee and the Treasury remain free to put different proposals before the Royal Commission on the Civil Service. "This particularly applies to the rates of pay for senior and principal medical officers the increases in which both sides regard as purely token." Neither the recent increases in the salaries of hospital doctors nor any other change in the remuneration of medical work outside the Civil Service will be made the basis of a claim to the Treasury before the Royal Commission's report is published; but this in no way limits either party's freedom to use any such factors in its submissions to the Royal Commission, or to use any other new considerations in fresh representations either before or after the Royal Commission has reported.

The scale now agreed for the basic grade is not to be regarded as establishing any particular relativity between that grade and any non-medical grade in the Civil Service.

In England Now

A Running Commentary by Peripatetic Correspondents

ONE of the pleasures of Professor Aird's film on the *Conjoined Twins of Kano* lay in following the investigations which established, before operation, which structures did and which did not connect the infants. Simple palpation was most important, but radiological, electrocardiographic, and radioactive isotopic methods also provided essential information. As a physician, I may say that I think that surgeons often have a lot to teach us in the use of direct, intelligent step-by-step elucidation of clinical problems. But surgeons have no monopoly. The morning after I saw the film I went to the garage in my car, which was making a new noise, like water running into a deep cistern. Not very loud, but I feared what it might portend, and like a mother with her child I wanted reassurance. Nevertheless I behaved correctly and consulted the vehicle's usual attendant, although I knew his liking for gloomy prognosis. He listened. "Specialist job," he said.

The specialist was of middle age and below medium height, clothed in an immaculate white gown like those worn by some doctors in hospitals in France. He asked me what was the matter. "It's the noise," I said, "transmission, I think." He listened there and here. "Probably magneto or water pump. Can you spare five minutes?" "Well, yes, but I can't spare half an hour. I have to go to hospital." "When we say five minutes we mean only six," he replied with a smile—a model for every consultant who wishes to temper authority with humour.

Two assistants in brown overalls arrived, towels were draped over the mudguard and in no time the fan-belt was off. I started the engine, the noise had gone. "Yes, magneto or water-pump. Joe, would you mind fetching the stethoscope? The telescopic one as well as the other. Thank you so much. And Bill, would you put the fan-belt on again?" The monaural telescopic and the binaural ordinary one arrived. The ear-pieces of the latter looked just like mine, except that the nickel plate was not flaking off and the rubber tubing was clean. The chest-piece, if I may so call it, bore a narrow metal rod about six inches long. The specialist applied its tip here and there systematically, with the engine running. "Yes," he said, removing the stethoscope, "water-pump. Now we'll order the replacement and you bring her in on Monday."

I should not push the surgical analogy too far, but I must admit that I paid no fee for the consultation and expect a whopping bill for the operation.

* * *

It is all very well for you, Sir, to affirm editorially that "enteric infections due to bathing beyond reasonable doubt are few," but you have not attempted to answer the really ticklish question of when a bather can be said to have bathed beyond reasonable doubt. Any wretched member of the party who gets up early may appear before breakfast looking virtuous and wringing out a wet bathing suit for all to see, but such evidence is obviously suspect. Unfortunately no-one has really ever defined the borderline between paddling and bathing. I would put the line at the pubis. The shock I get when the first wave splashes my perineum is something quite distinct from paddling, but if one retreats at this stage I'm afraid there is still reasonable doubt about the bathe. Some would accept a wet abdomen; others demand a wet neck or even wet hair; but no doubt, allowing for enteric, the editorial criterion would demand total immersion with a good swallow of sea water.

* * *

I often breathe a sigh of relief that Jim Dale and his partner seem to cope so effectively with the ailments of Parkwood Hill; Mrs. Mountford would be off my list after the first quarter. I should hate to be called in to attend the Huggetts, and if the Archers lived a bit nearer they would find me very short-tempered with Philip at times. But no practice can thrive on such a negative philosophy, so there are now seven new names on my list since the cards for the Grove Family arrived this month.

You know how it is when you take on a new family; you tend to make a snap judgment of their relative nuisance values to the practice. The Grove household shows all the signs of being another matriarchy, with weekly anarchical fugues, so the prognosis seems likely to follow the basic patterns of petticoat rule. Grandma's autocratic hold is getting shaky and it obviously won't be long before I am digging the Authorised Officer out of bed to cope with the old girl's senile dementia. Mrs. Grove is shaping up pretty fast to take on Grandma's crown while it is still warm.

Both Mr. and Mrs. Grove carry enough middle-aged spread to make constant demands for 'Dexedrine' a dead cert within the next six months, and I suspect that Mrs. G. is going to be rather tiresome to steer through her looming menopause on account of the psychosomatic factors in the household.

Mr. Grove suffers from the initial disability of not being master in his own house, and if I can manage to sustain him from anxiety neurosis I rather fear that he will throw a duodenal ulcer on us.

On the whole I feel confident that I can grapple with the more mature members of the Grove Family, but the kids would make any G.P. wonder if they are worth their capitations. That scrounger Jack reminds me of my Service days; M and D for you, my lad! And let's hope that the Army knocks a bit of sense into you where your father has obviously failed. Pat is going to be hard to convince that a lot more early nights and a lot more protein in her lunches would be better than burning the candle at both ends. I won't be able to do much for her shallow mind, but I really would like to keep tubercle out of her apices until the penny drops and she settles down. Daphne is my main hope despite her tender years. I think I shall have to take her into consultation to get the low-down on the rest of the family. And then there is Lennie—the sooner we ship him and his behaviour problems off to the nearest child-guidance clinic the better, otherwise the poor tax-payer will have to find another £6 10*s.* a week to keep him in an approved school.

Well, there they are, seven little cards beaming at the kindly executive council, seven more wrinkles to furrow a practitioner's weary brow, seven more peripheral grey hairs. Look in and see for yourself the wealth of clinical material while I try and find an easier way of earning a living.

* * *

The other evening, on my return home from work, late and exhausted, my wife said: "You know, doctors are paid too much." I digested this awhile, and after due thought replied: "I think you mean that teachers are not paid as much as they should be?" "Exactly."

Ruminating upon my correct interpretation of her remark I came to the conclusion that she probably needed a new evening dress. To confirm the diagnosis, I remarked: "By the way, you know it's three years since I had a new suit? Do you think I can go on much longer in this one?" "Well, you are whole-time, and you're an S.H.M.O. . . ." I accepted both rebukes, and at that moment the B.B.C. announced the magnificent award to hospital staff. "There you are," says she, "you'll get at least £50 more: surely you aren't so mean as all that?"

During the past week she has ordered: (1) a new car at £550; (2) an evening dress at £31 10*s.*; (3) an alteration to her fur coat at "approx. £28"; (4) a new shirt for me at £3 3*s.*

* * *

My assistant and I bent over the foul-smelling post-mortem. The surgical registrar who was looking on fished his pipe out of his pocket and lit it. But presently it was too much even for him and he walked out. As the door closed behind his back, my assistant heaved a great sigh of relief. "Thank goodness," he said, "that fellow has taken his pipe away."

* * *

Clinician: Why are you looking at those skin biopsies?

Pathologist: I'm trying to sex them by this new-fangled idea of studying the nuclear chromatin.

Clinician: Then you will issue a Skinsey report I suppose?

Letters to the Editor

TUBERCULOSIS IN ADOLESCENCE

SIR,—The recent Ministry of Health circular,[1] to which you refer in your leader of April 17, calls for action.

Some may think that we have hardly reached the point when tuberculosis can be dealt with on epidemiological lines like smallpox or typhoid fever; but all will agree that new and greater effort is called for in many branches of our anti-tuberculosis organisation. A vigorous drive is certainly needed to diagnose the disease more often in its earliest stages.

I have been impressed, in recent years, by the finding of adult-type disease in school-children who happen to have been examined by mass radiography. The disease in adolescence has a strong tendency towards inevitable deterioration if energetic measures are not taken. If the disease in young people is not dealt with at an early stage, treatment will, in most cases, be demanded in later years when the chances of success may be much reduced.

Among 14-year-olds mass radiography reveals 1·1 new cases of active tuberculosis per 1000 boys and 1·7 per 1000 girls,[2] but the method has so far only been applied in a patchy way. Has not the time arrived to extend the use of mass radiography in young people towards the end of their school careers? Such a proposal is hardly new, for a scheme of this sort was advanced in 1936 by Wingfield and Macpherson.[3]

Another recent Ministry circular,[4] which gives local authorities powers to inoculate 13-year-olds with B.C.G. vaccine, points the way. Local authorities who implement the new scheme will find that approximately 40% of children have already been infected with tuberculosis. It is very much to be hoped that these children will be promptly radiographed, for it is certain that they will provide a useful harvest of early cases of pulmonary tuberculosis, many of adult type. Obviously, all the cases which may be revealed by mass radiography will be in this 40% who are already tuberculin reactors. It is likely that, taking one year of age only (say, 13 or 14), a single careful examination would bring to light 18 new cases of active tuberculosis in every million of the population (approximately 13,000 children at, say, 1·4 per thousand); and it would only be necessary to radiograph approximately 5000—the 40% known reactors. It is to be hoped that local authorities and regional hospital boards will consider what this would mean in their own areas and decide that it is both practicable and worth while.

Pulmonary tuberculosis of adult type in young people has, in the past, generally been so scattered that few can claim much experience with this age-group. My colleagues and I have recently reported[5] on 116 such cases treated in a sanatorium for long periods and subsequently followed up for an average of over six years. Collapse therapy was used extensively, but antibiotics were not yet available. Selected cases did well with an artificial pneumothorax, but the over-all results left much to be desired. Long-term investigation of a more recent series would probably show greater improvement with modern chemotherapy. So far, however, there can be no final decision on the most effective therapy. Many adolescents will certainly require sanatorium treatment, perhaps combined with antibiotics and collapse or resection. Treatment should be undertaken only in centres where adequate education can be given. Possibly some youngsters may be allowed to continue, under expert supervision, at ordinary schools. Special registers of these cases should, in any event, be compiled in appropriate areas so that they can be followed up in groups large enough for helpful analysis. In this way knowledge would be gained not only of the disease in school-children, but of its often insidious development in young adults.

High Wood Hospital for Children,
Brentwood, Essex. F. J. BENTLEY.

1. Prevention of Tuberculosis. Circular H.M.(54)30.
2. Report of the Ministry of Health, 1952.
3. Wingfield, R. C., Macpherson, A. M. C. *Brompton Hosp. Rep.* 1936, **5**.
4. Circular 324/B.C.G., 1953.
5. Bentley, F. J., Grzybowski, S., Benjamin, B. Tuberculosis in Childhood and Adolescence. London, 1954.

SPREAD OF INFLUENZA IN THE HOUSEHOLD

SIR,—The paper from Cirencester by Dr. Hope Simpson and Dr. Sutherland in your issue of April 3 is a most interesting example of the information which can be gathered by careful observations on that fundamental epidemiological unit—the family or household. The success of timing of the occurrence of cases of an infectious illness as a means of proof of the mode of contagion must, however, depend upon the accuracy of the recognition of each infection. The latter, in turn, calls for a recognisable clinical phenomenon as an accompaniment of infection, or else must be based upon laboratory findings.

Diseases such as measles, which exhibit characteristic rashes, thus afford good material for analysis, and it is hardly surprising that the actual occurrence of cases in the family agrees so well with the predicted numbers based upon a person-to-person chain of infection.

Similar observation on cases of influenza is handicapped in two ways: firstly, by the occurrence of other febrile respiratory diseases resembling influenza but not due to the influenza viruses; and, secondly, by the known frequency of subclinical infection as a result of exposure to influenza viruses. The first difficulty would be likely to obscure the findings by inflation of the figures for the number of cases in the household, whereas the second one might prevent the expected wave of secondary cases because of the exhaustion of susceptibles by this mode of infection. Whether or not these arguments are valid as an explanation of the irregularity of the influenza data presented by Dr. Hope Simpson and Dr. Sutherland, it would seem necessary to urge the need for laboratory confirmation of the occurrence of infection in future studies of this kind. Nevertheless, the variable pattern of behaviour of influenza, as judged on a purely clinical basis such as the authors describe, is in keeping with the variable epidemiological pattern seen in the community as a whole, and also, may it be added, with the remarkable variability of the characters of the causative viruses and of the still-undefined human properties of susceptibility or resistance to their attack.

University Department of Medicine,
The Royal Hospital,
Sheffield, 1. C. H. STUART-HARRIS.

TREATMENT OF VARICOSE ULCERS

SIR,—I would like to support Mr. Murley (April 10) in his criticisms of some of Mr. Lee's suggestions (April 3) for the treatment of "varicose" ulceration. Arterial spasm plays a very small part in the causation of the vast majority of varicose ulcers, a fact which was well demonstrated by Brewer[1] of Liverpool. In his series he proved by arteriovenograms that the ulcer which was due to arterial spasm was rare. It is in this small group that sympathectomy, or the alternative of injection of the femoral artery with tolazoline, might possibly give some benefit. It is to be hoped, however, that Mr. Lee will confine sympathectomy and injection of the femoral artery to this rare group and that the remainder will receive the accepted treatment, whose benefits we all understand so well.

1. Brewer, A. C. *Lancet*, 1951, ii, 177.

Compression treatment is the sheet anchor in the treatment of varicose ulceration. This fact has been shown to us throughout the ages, especially by Thomas Baynton in the eighteenth and Benjamin Brodie in the nineteenth centuries. Recently we have to thank Bisgaard for calling our attention to the immense value of physiotherapy, and Cockett and Elgan Jones [2] for simplifying what they term so aptly "the ankle blow-out syndrome." The skill in healing thrombotic ulcers lies in the correct timing of *when* to use these three cardinal factors in treatment. As a rule, compression will give us a slim and healed limb; massage will then still further improve the leg; and finally the removal of the "short-circuited circulation" above and around the ankle will complete the treatment, even though in certain cases a changed "way of life" may be required.

London, W.1. R. ROWDEN FOOTE.

REMUNERATION OF HOSPITAL MEDICAL STAFF

SIR,—I have been wondering why I am pleased with the recent award of pay increases to hospital medical staff, while so many of my colleagues feel that it is not enough. I have now realised that when I became a tuberculosis officer in 1941 my income was £600–800 per annum, and now, though graded S.H.M.O., it will be £1500–1950—a betterment factor of 150%. There must be others with a similar experience.

Clearly, some redistribution of income within the profession has been taking place, and viewed dispassionately this would not seem to be a bad thing. The justification for very large incomes for consultants in the past was surely in the lean years, during which their incomes varied from nothing as a houseman to the odd hundred or two as a registrar later on. The path has been made easier, though perhaps, as a result, the competition is now fiercer. Surely the demand for 100% increase for everybody is unrealistic and would only perpetuate the injustice to the lower-paid ranks. The negotiators have done well, in my opinion, to distribute the available sum where it will be most appreciated.

When we compare ourselves with the general practitioners, there is room for disappointment, especially as the hospital medical staff award is not retrospective to 1948. But again, as you say in your leader of April 10, future experience will show whether the correct balance will be found, and sufficient recruits attracted to all sides of the profession. The Cinderella of the health service now is Public Health, and every effort should be made to help our colleagues there in this just claim.

Liverpool, 18. WILLIAM D. GRAY.

SIR,—The majority of S.H.M.O.s occupy posts carrying full clinical responsibility, and in fact work as consultants. We must have considerable value as "cheap labour" in the National Health Service. Unfortunately, we have little or no bargaining-power, and our posts could easily be filled by registrars in search of financial security. Could this be why we have received an increase in our rate of pay of 15·4% as against 23·5% for the consultants?

Queen Alexandra Hospital, Cosham, Portsmouth. A. M. READ.

SIR,—Surely we are all agreed that the award which junior hospital doctors have just received is ridiculously inadequate. It is neither retrospective nor untaxed, and bears no relation to the increase in the cost of living since 1948.

If this award goes unchallenged we shall probably receive another £75 or £100 in 1960! It is understandable that each section of the profession has its own economic interest at heart, but if these token awards are to be stopped, the B.M.A., in its proper rôle of a trade union, must press the claims of each section of the profession as a whole, and refuse piecemeal settlements, such as the Danckwerts award, which leave the claims of other sections of the profession unsettled.

Only when this happens will we be able to reject these awards, knowing we are in a strong enough position to do so.

Norwich. J. M. BROWNLIE.

SIR,—Now that salary increases for hospital medical staff and consultants have been finally agreed on, is it not high time National Service medical officers' pay was increased? Recent Service increases expressly omitted National Servicemen.

One reason that National Servicemen are not paid so much as their Regular contemporaries is to try to persuade some to apply for permanent commissions; but we, especially those who are married and trying to build up some sort of home, have to exist in comparative penury. There are no allowances in lieu of married quarters (no accommodation is provided for National Service medical officers) and the marriage allowance is less (two-thirds) than for Regulars.

At one time the rates of pay of house-officers and National Servicemen may have been adjudged to approximate (with the perquisites available to some house-officers the difference was greater), but now this can no longer be true, especially for any who held senior house-officer posts prior to call-up.

NATIONAL SERVICEMAN.

REPAIR OF LARGE HERNIÆ

SIR,—Your issue of Feb. 20, containing Professor Stock's account of the use of nylon mesh in the treatment of inguinal herniæ, has just arrived.

"The use of implants of foreign material," he says, "is almost as old as the history of operations for hernia . . . but most attempts have failed because of undesirable tissue reactions and sepsis." Surely there is only one type of tissue reaction to the introduction of any sterile foreign material into the human body—an aseptic inflammatory response that may or may not proceed to pus formation irrespective of actual infection introduced at the time of operation. Indeed, the essence of all operations of this type is the induction of just this type of response, with the production of a strong fibrous wall which, it is hoped, will take the place of the weakened muscles in the posterior inguinal wall.

Perhaps the greatest weakness of all "implant" operations, applied to indirect inguinal herniæ, is that they concentrate attention on the repair of the posterior inguinal wall, instead of on the re-creation of a functioning internal ring. But, as Ogilvie pointed out many years ago, in indirect herniæ the primary site of weakness is not the posterior wall but rather the stretched, weakened internal ring. Professor Stock does not say how many of his "ten patients with inguinal hernia" actually had indirect herniæ, but he implies that his operation may be used equally well for either direct or indirect. Surely there is a distinction to be made between the two.

He adds that "if the testis is abnormal or there is a thick hydrocele sac, orchidectomy is usually performed," which is a curious statement in this context. If an indirect hernia has reached such a stage that the internal ring and the posterior inguinal wall cannot be functionally re-formed, then the prospect has to be considered of complete closure of the canal, usually (though, as Aird points out, not necessarily) with orchidectomy. This, like all other forms of herniorrhaphy, does not guarantee against recurrence; and the patient, as well as the surgeon, must weigh the relative advantages which orchidectomy and complete closure of the canal offer. But in the treatment of hernia, it is the hernia that determines the necessity or otherwise of orchid-

2. Cockett, F. B., Elgan Jones, D. E. *Ibid*, 1953, i, 17.

ectomy, and not the state of the testis, let alone the state of the sac or tunica. To say that orchidectomy is usually done "if the testis is obviously abnormal" is surely irrelevant in this context: to say that it is usually done if "there is a thick hydrocele sac" is a little radical. When else would one do an orchidectomy for hydrocele?

Inexpensive, ubiquitous, malleable, and indestructible, nylon may be; and it is perhaps some comfort to know that when we have shuffled off our mortal soles the immortal uppers will still live on: but will they help my hernia?

Methodist Mission Hospital,
Ilesha, Nigeria. H. J. WRIGHT.

IDENTIFICATION OF DRUGS

SIR,—We are interested in the letter from Dr. King, in your issue of April 10.

This company manufactures its tablets with an identification mark, and we issue, on request, details showing which marks coincide with which drugs. Furthermore, in our advertisements in the medical press, we often show a picture of the actual tablet so that doctors may become familiar with the marking on the tablet. We know that some other manufacturers adopt somewhat similar policies.

Bayer Products Ltd.,
London, W.C.2. L. M. SPALTON
Director.

TREATMENT OF DEAFNESS

SIR,—In your issue of March 13, Mr. Robin warns the medical profession and its hard-of-hearing patients against "claims made for improved hearing by re-education methods."

It seems that he has, once again, confused the purely physical ability to hear with hearing in its broadest sense—namely, the ability of the cerebral cortex to interpret and respond to the auditory signals it receives from the ear in the course of daily hearing.

It is hard to say why Mr. Robin wishes to give your readers the impression that auditory training is said to improve the patient's physical ability to hear, when no such claim has been made. The very term implies that auditory re-education deals solely with cortical hearing. Obviously there is no simple, single, "scientific" test or measurement for a complex function which embraces a wide variety of auditory achievements such as recognition, discrimination, reaction-time, and memory for an endless variety of sounds received under dozens of different conditions, and which, in the hard-of-hearing, is further governed by fear, doubt, fatigue, lack of confidence, and even personality change.

Yet Mr. Robin demands that these aspects of hearing, and any change therein, be gauged by tests designed solely for gauging physical change in the peripheral auditory mechanism. Without such "scientific proof," he says, there can be no improvement in hearing, even though the patient's relations, associates, or employers state freely that it is very evident that the patient hears better. When confronted with such evidence, Mr. Robin mistakes cause for effect and seeks refuge in the suggestion that the patient's ability to "listen" has improved, even though we have painstakingly shown him that the improvement included sounds and conversations for which the patient could not possibly be listening.

As an aural surgeon, Mr. Robin must recall that the rather unscientific "social adequacy index" was adopted to assess hearing improvement in fenestrated cases, simply because pure tone and speech audiometry too often failed to portray the clinical results.

At this unit we assess improvement by what, in our opinion and long experience, is the most comprehensive way of depicting the results of auditory rehabilitation—the hearing disability questionnaire. This lists and indicates graphically the patient's stated ability before and after re-education for: conversation across a desk and a room, round a table, and in groups; speech and sounds other than speech (bells, buzzers, sounds from behind him, and from room to room); telephone, television, radio, confidential tones, whispered speech, and so on. Mr. Robin makes no mention of this in his letter. It might interest him to know, and to inquire why, the results of rehabilitation of the orthopædically handicapped are also assessed and recorded in such homely and "unscientific" terms as "turning over in bed," "combing and brushing the hair," "drinking from a glass," "walking up and down stairs," "striking a match," and so on.

The tone of his letter implies that auditory re-education is a worthless quackery whose "principle needs medical and scientific investigation before the practice is recognised as of true value," when in fact its use, both with and without hearing-aids, has long been practised in many of the most important auditory rehabilitation centres of the world.

Mr. Robin's motives are not to be questioned, but it is to be regretted that he has seen fit to voice his opinion publicly and dogmatically on the worth of a very specialised field of endeavour—after only a half-hour's exposure to it. In seeking to protect the hard-of-hearing public from being exploited, he has only succeeded in directing them away from the type of help they so sorely need. We trust that this letter will be able to undo the harm.

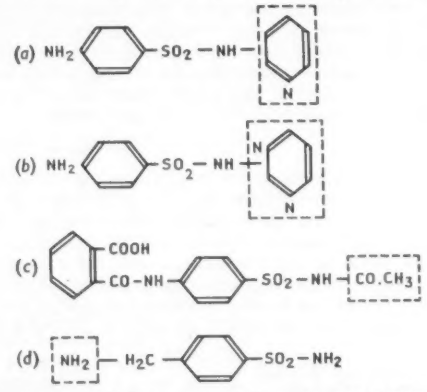
Ardente Audiotherapy Unit,
London, W.1. ELIZABETH CHADWICK.

CHEMICAL STRUCTURE OF SULPHONAMIDES AND THEIR EFFECT ON PERISTALSIS

SIR,—The effect of phthalylsulphacetamide on intestinal peristalsis was mentioned in your journal last year [1]; so I am writing to draw your attention to some experiments done in Germany. These have shown that the action of various sulphonamides on peristalsis is closely related to their structure.

Enders [2 3] and Kleibel [4 5] have found that certain groups of sulphonamides inhibit peristalsis, apart altogether from their antibacterial action in intestinal infections.

Sulphathiazole ('Cibazole,' 'Eleudron'), sulphapyridine ('Eubasine'), and phthalylsulphathiazole [6] ('Taleudron') inhibit peristalsis in experimental concentrations of about 1 : 2000, which should be attained with a dosage of 8–10 g. daily in the human subject. Their chemical structure shows a benzolsulphonamide group attached to a ring containing a single N-atom (fig., *a*). If benzolsulphonamide is combined in a molecule with a ring carrying a double N-atom (*b*), as in sulphapyrimidine ('Debenal') or sulphadiazine, or if this ring is replaced by



an aliphatic chain (*c*), as in sulphacetamide ('Albucid'), sulphaguanidine, and phthalylsulphacetamide, peristalsis is inhibited only at an experimental concentration of about 1 : 500, which would require a dosage of 36–40 g. daily in man. In other words, the quantity needed to inhibit peristalsis has to be four times as great.

1. *Lancet*, 1953, i, 831.
2. Enders, A. *Dtsch. med. Wschr.* 1951, **76**, 1404.
3. Enders, A. *Dtsch. Z. Verdau. Stoffwechselkr.* 1953, **13**, 236; *Arch. exp. Path.* 1943, **201**, 366.
4. Kleibel, F. *Dtsch. Z. Verdau. Stoffwechselkr.* 1952, **12**, 257.
5. Kleibel, F. *Ibid*, p. 183.
6. Henning, N. *In* von Bergmann, Frey, and Schwiegk's Handbuch der Inneren Medizin. Berlin, 1952; vol. III, part 2, p. 37.

Finally there is another sulphonamide, aminomethylbenzolsulphonamide (' Marfanil '), which has been shown both experimentally and clinically to excite peristalsis instead of inhibiting it. This preparation differs from those previously mentioned in having an NH_2 group joined to its benzole ring by a methyl group (*d*). It is interesting to note that it also differs from the others in its effect on intestinal bacteria.

These actions were demonstrated on the gut of rat and guineapig, and they did not persist longer than one hour. Desensitisation may thus be ruled out.

Medical Polyclinic,
Würzburg University. FRANZ KLEIBEL.

THE RECENT BURN

SIR,—Correspondents have lately discussed the desirability of leaving blisters intact when dealing with minor burns in industry. I have found that undiluted 1% electrolytic sodium hypochlorite solution, applied immediately in the form of a compress, prevents the formation of blisters; or if they have already formed on a recent burn, they are quickly reduced. Since the skin remains unbroken, there is absolutely no risk of infection with this method; moreover, it takes very little time, and pain is much reduced. If the skin is broken, the hypochlorite should be diluted to form an isotonic solution.

London, W.1. M. MARGARET DURRANT.

TREATMENT OF THYROTOXICOSIS WITH POTASSIUM PERCHLORATE

SIR,—We should be grateful if you would allow us to add a postscript to our article of April 10. We there described a patient whose gastric symptoms became much worse when her treatment was changed from methyl thiouracil (50 mg. daily) to potassium perchlorate (100 mg. daily). The dyspepsia disappeared when she was put back on methyl thiouracil, but reappeared a second time when potassium perchlorate was given. She was known to have a diaphragmatic hernia, and we concluded that perchlorate was probably irritating an already inflamed gastric mucosa.

Further experience with this patient makes this conclusion unlikely.

After another period on methyl thiouracil the gastric symptoms again increased, and became incapacitating. They mainly occurred when she went to bed at night, and consisted of severe epigastric pain and vomiting. These symptoms were only partially controlled by outpatient therapy and she was admitted to hospital. After a few days' treatment by posture, diet, and alkalis the symptoms rapidly subsided, and we took the opportunity of testing the effect of potassium perchlorate under controlled conditions.

For four consecutive 5-day periods she was given tablets of identical appearance, labelled A, B, C, and D, to be taken twice daily. Tablets A and C contained lactose only, tablets B and D contained 200 mg. of potassium perchlorate. The content of the tablets was not known to the patient, the nursing staff, or the clinical clerk who recorded the symptoms daily. During the 20-day test period only one attack of epigastric pain and vomiting occurred. This happened while she was taking tablet A (lactose). At the time of the test potassium perchlorate clearly did not irritate her gastric mucosa, although gastric symptoms had recently been present and the mucosa might be expected to be in a sensitive state. It seems probable that the exacerbations of dyspepsia twice observed in the past when she was taking potassium perchlorate were not caused by the drug.

This was the only case, out of 108, in which there seemed to be good evidence of gastric irritation by potassium perchlorate. Since further experience has shown that this evidence was probably misleading, it now seems unlikely that potassium perchlorate will prove to be a gastric irritant, although this possibility must still be kept in mind.

University College Hospital
Medical School, London. M. E. MORGANS
W. R. TROTTER.

METHYLPENTYNOL AS A HYPNOTIC FOR OLD PEOPLE

SIR,—Most elderly patients require some artificial aid to sleep, but the range of suitable hypnotics for routine use is very limited. The drugs commonly used include paraldehyde, chloral hydrate, sodium bromide, the traditional "Mist. Three-fifteens," and—most widely used of all—the barbiturates (mainly the "medium-acting" and "short-acting" ones). For old patients nearly all these hypnotics have some disadvantages.

I would like to report a trial of a comparatively new hypnotic drug, methylpentynol (' Oblivon '). Although its chemical structure bears superficial resemblances to paraldehyde and to methyl alcohol, methylpentynol is a separate drug in its own right. Methylpentynol (methylparafynol in U.S.A.) is a simple unsaturated aliphatic carbinol, 3-methyl-pentyne-ol-3, having the structural formula: $CH{:}C.C(CH_3)(OH).CH_2.CH_3$.

The literature on this drug has been reviewed [1] but, with the exception of a limited study of the drug in fifty-two psychiatric patients aged 61 and over,[2] the usefulness of methylpentynol as a mild hypnotic for the elderly has received little attention.

All the patients studied were aged 65 years or over. The report is based on a series of ninety-four patients, of whom thirty-two were aged 65–74, forty-three aged 75–84, and nineteen aged 85 or more. There were twenty-eight men and sixty-six women. All were general hospital patients and were under continuous observation, day and night. The great majority had required regular dosage with other commonly used hypnotics, with variable effect and for varying periods, up to the time of beginning methylpentynol treatment. Only those who received the drug continuously for a minimum period of 7 days or more were included in this study: thirty-eight patients received the drug nightly for 21 days or more, and twelve for 42 days or more. The minimum total dosage was 6·7 g., the maximum 144 g. The longest trial was in a man aged 76 who received a total of 144 g. over a continuous period of 72 days.

Method of Administration.—The unit dose of methylpentynol is 250 mg., and this was incorporated in one drachm of elixir specially prepared by the manufacturers. Any drug, if sufficiently soluble in water and not objectionable in taste, is more conveniently given to old people in liquid form rather than as tablets or capsules. The crude drug, methylpentynol, is a volatile liquid with a vile burning taste, far worse than paraldehyde, and it was therefore originally dispensed in capsules. For the purpose of this study, however, it was incorporated in an elixir, which disguised its taste. The most effective dose was 4–6 drachms (1·0–1·5 g.). Smaller doses seldom had a hypnotic effect, and larger doses had no added advantage. Altogether, forty-four patients received a dose of 4 drachms nightly for periods varying from 7 to 59 days; forty-eight were given a nightly dose of 6 drachms for periods of 7 to 49 days, and twelve were given a dose of 8 drachms nightly for periods ranging from 12 to 72 days.

Assessment of Efficiency.—The effectiveness of the drug on each individual was observed by doctors and by senior nurses, who also recorded every half-hour during the night whether or not the patient was asleep. Special charts were used and records were kept every night while the drug was being given. After the trial, the hypnotic effect for any night was noted as "good" if after the dose had been given the patient had been asleep within 1 hour, and had remained asleep for at least 5 hours. The response was noted as "poor" if sleep was broken, or had not ensued within 2 hours of giving the drug, regardless of the duration of sleep. In any particular patient, the drug was said to have been "efficient" if a "good" night's sleep was obtained on 70% or more of the nights on which it was given.

Results.—In sixty-one of the ninety-four patients (64%), the drug was found to be "efficient." Its prolonged use gave no troublesome side-effects, and there has been no evidence of addiction. When the hypnotic effects wear off, patients remain quietly sedated and do not become restless or noisy, so there is usually no need to repeat the dose during the

1. *Brit. med. J.* 1953, ii, 435.
2. May, P. R. A., Ebaugh, F. G. *J. Amer. med. Ass.* 1953, **152**, 801.

Letters to the Editor

TUBERCULOSIS IN ADOLESCENCE

SIR,—The recent Ministry of Health circular,[1] to which you refer in your leader of April 17, calls for action.

Some may think that we have hardly reached the point when tuberculosis can be dealt with on epidemiological lines like smallpox or typhoid fever; but all will agree that new and greater effort is called for in many branches of our anti-tuberculosis organisation. A vigorous drive is certainly needed to diagnose the disease more often in its earliest stages.

I have been impressed, in recent years, by the finding of adult-type disease in school-children who happen to have been examined by mass radiography. The disease in adolescence has a strong tendency towards inevitable deterioration if energetic measures are not taken. If the disease in young people is not dealt with at an early stage, treatment will, in most cases, be demanded in later years when the chances of success may be much reduced.

Among 14-year-olds mass radiography reveals 1·1 new cases of active tuberculosis per 1000 boys and 1·7 per 1000 girls,[2] but the method has so far only been applied in a patchy way. Has not the time arrived to extend the use of mass radiography in young people towards the end of their school careers? Such a proposal is hardly new, for a scheme of this sort was advanced in 1936 by Wingfield and Macpherson.[3]

Another recent Ministry circular,[4] which gives local authorities powers to inoculate 13-year-olds with B.C.G. vaccine, points the way. Local authorities who implement the new scheme will find that approximately 40% of children have already been infected with tuberculosis. It is very much to be hoped that these children will be promptly radiographed, for it is certain that they will provide a useful harvest of early cases of pulmonary tuberculosis, many of adult type. Obviously, all the cases which may be revealed by mass radiography will be in this 40% who are already tuberculin reactors. It is likely that, taking one year of age only (say, 13 or 14), a single careful examination would bring to light 18 new cases of active tuberculosis in every million of the population (approximately 13,000 children at, say, 1·4 per thousand); and it would only be necessary to radiograph approximately 5000—the 40% known reactors. It is to be hoped that local authorities and regional hospital boards will consider what this would mean in their own areas and decide that it is both practicable and worth while.

Pulmonary tuberculosis of adult type in young people has, in the past, generally been so scattered that few can claim much experience with this age-group. My colleagues and I have recently reported[5] on 116 such cases treated in a sanatorium for long periods and subsequently followed up for an average of over six years. Collapse therapy was used extensively, but antibiotics were not yet available. Selected cases did well with an artificial pneumothorax, but the over-all results left much to be desired. Long-term investigation of a more recent series would probably show greater improvement with modern chemotherapy. So far, however, there can be no final decision on the most effective therapy. Many adolescents will certainly require sanatorium treatment, perhaps combined with antibiotics and collapse or resection. Treatment should be undertaken only in centres where adequate education can be given. Possibly some youngsters may be allowed to continue, under expert supervision, at ordinary schools. Special registers of these cases should, in any event, be compiled in appropriate areas so that they can be followed up in groups large enough for helpful analysis. In this way knowledge would be gained not only of the disease in school-children, but of its often insidious development in young adults.

High Wood Hospital for Children,
Brentwood, Essex. F. J. BENTLEY.

1. Prevention of Tuberculosis. Circular H.M.(54)30.
2. Report of the Ministry of Health, 1952.
3. Wingfield, R. C., Macpherson, A. M. C. *Brompton Hosp. Rep.* 1936, 5.
4. Circular 324/B.C.G., 1953.
5. Bentley, F. J., Grzybowski, S., Benjamin, B. Tuberculosis in Childhood and Adolescence. London, 1954.

SPREAD OF INFLUENZA IN THE HOUSEHOLD

SIR,—The paper from Cirencester by Dr. Hope Simpson and Dr. Sutherland in your issue of April 3 is a most interesting example of the information which can be gathered by careful observations on that fundamental epidemiological unit—the family or household. The success of timing of the occurrence of cases of an infectious illness as a means of proof of the mode of contagion must, however, depend upon the accuracy of the recognition of each infection. The latter, in turn, calls for a recognisable clinical phenomenon as an accompaniment of infection, or else must be based upon laboratory findings.

Diseases such as measles, which exhibit characteristic rashes, thus afford good material for analysis, and it is hardly surprising that the actual occurrence of cases in the family agrees so well with the predicted numbers based upon a person-to-person chain of infection.

Similar observation on cases of influenza is handicapped in two ways: firstly, by the occurrence of other febrile respiratory diseases resembling influenza but not due to the influenza viruses; and, secondly, by the known frequency of subclinical infection as a result of exposure to influenza viruses. The first difficulty would be likely to obscure the findings by inflation of the figures for the number of cases in the household, whereas the second one might prevent the expected wave of secondary cases because of the exhaustion of susceptibles by this mode of infection. Whether or not these arguments are valid as an explanation of the irregularity of the influenza data presented by Dr. Hope Simpson and Dr. Sutherland, it would seem necessary to urge the need for laboratory confirmation of the occurrence of infection in future studies of this kind. Nevertheless, the variable pattern of behaviour of influenza, as judged on a purely clinical basis such as the authors describe, is in keeping with the variable epidemiological pattern seen in the community as a whole, and also, may it be added, with the remarkable variability of the characters of the causative viruses and of the still-undefined human properties of susceptibility or resistance to their attack.

University Department of Medicine,
The Royal Hospital,
Sheffield, 1. C. H. STUART-HARRIS.

TREATMENT OF VARICOSE ULCERS

SIR,—I would like to support Mr. Murley (April 10) in his criticisms of some of Mr. Lee's suggestions (April 3) for the treatment of "varicose" ulceration. Arterial spasm plays a very small part in the causation of the vast majority of varicose ulcers, a fact which was well demonstrated by Brewer[1] of Liverpool. In his series he proved by arteriovenograms that the ulcer which was due to arterial spasm was rare. It is in this small group that sympathectomy, or the alternative of injection of the femoral artery with tolazoline, might possibly give some benefit. It is to be hoped, however, that Mr. Lee will confine sympathectomy and injection of the femoral artery to this rare group and that the remainder will receive the accepted treatment, whose benefits we all understand so well.

1. Brewer, A. C. *Lancet*, 1951, ii, 177.

Compression treatment is the sheet anchor in the treatment of varicose ulceration. This fact has been shown to us throughout the ages, especially by Thomas Baynton in the eighteenth and Benjamin Brodie in the nineteenth centuries. Recently we have to thank Bisgaard for calling our attention to the immense value of physiotherapy, and Cockett and Elgan Jones [2] for simplifying what they term so aptly "the ankle blow-out syndrome." The skill in healing thrombotic ulcers lies in the correct timing of *when* to use these three cardinal factors in treatment. As a rule, compression will give us a slim and healed limb; massage will then still further improve the leg; and finally the removal of the "short-circuited circulation" above and around the ankle will complete the treatment, even though in certain cases a changed "way of life" may be required.

London, W.1. R. ROWDEN FOOTE.

REMUNERATION OF HOSPITAL MEDICAL STAFF

SIR,—I have been wondering why I am pleased with the recent award of pay increases to hospital medical staff, while so many of my colleagues feel that it is not enough. I have now realised that when I became a tuberculosis officer in 1941 my income was £600–800 per annum, and now, though graded S.H.M.O., it will be £1500–1950—a betterment factor of 150%. There must be others with a similar experience.

Clearly, some redistribution of income within the profession has been taking place, and viewed dispassionately this would not seem to be a bad thing. The justification for very large incomes for consultants in the past was surely in the lean years, during which their incomes varied from nothing as a houseman to the odd hundred or two as a registrar later on. The path has been made easier, though perhaps, as a result, the competition is now fiercer. Surely the demand for 100% increase for everybody is unrealistic and would only perpetuate the injustice to the lower-paid ranks. The negotiators have done well, in my opinion, to distribute the available sum where it will be most appreciated.

When we compare ourselves with the general practitioners, there is room for disappointment, especially as the hospital medical staff award is not retrospective to 1948. But again, as you say in your leader of April 10, future experience will show whether the correct balance will be found, and sufficient recruits attracted to all sides of the profession. The Cinderella of the health service now is Public Health, and every effort should be made to help our colleagues there in this just claim.

Liverpool, 18. WILLIAM D. GRAY.

SIR,—The majority of S.H.M.O.s occupy posts carrying full clinical responsibility, and in fact work as consultants. We must have considerable value as "cheap labour" in the National Health Service. Unfortunately, we have little or no bargaining-power, and our posts could easily be filled by registrars in search of financial security. Could this be why we have received an increase in our rate of pay of 15·4% as against 23·5% for the consultants?

Queen Alexandra Hospital,
Cosham, Portsmouth. A. M. READ.

SIR,—Surely we are all agreed that the award which junior hospital doctors have just received is ridiculously inadequate. It is neither retrospective nor untaxed, and bears no relation to the increase in the cost of living since 1948.

If this award goes unchallenged we shall probably receive another £75 or £100 in 1960! It is understandable that each section of the profession has its own economic interest at heart, but if these token awards are to be stopped, the B.M.A., in its proper rôle of a trade union, must press the claims of each section of the profession as a whole, and refuse piecemeal settlements, such as the Danckwerts award, which leave the claims of other sections of the profession unsettled.

Only when this happens will we be able to reject these awards, knowing we are in a strong enough position to do so.

Norwich. J. M. BROWNLIE.

SIR,—Now that salary increases for hospital medical staff and consultants have been finally agreed on, is it not high time National Service medical officers' pay was increased? Recent Service increases expressly omitted National Servicemen.

One reason that National Servicemen are not paid so much as their Regular contemporaries is to try to persuade some to apply for permanent commissions; but we, especially those who are married and trying to build up some sort of home, have to exist in comparative penury. There are no allowances in lieu of married quarters (no accommodation is provided for National Service medical officers) and the marriage allowance is less (two-thirds) than for Regulars.

At one time the rates of pay of house-officers and National Servicemen may have been adjudged to approximate (with the perquisites available to some house-officers the difference was greater), but now this can no longer be true, especially for any who held senior house-officer posts prior to call-up.

NATIONAL SERVICEMAN.

REPAIR OF LARGE HERNIÆ

SIR,—Your issue of Feb. 20, containing Professor Stock's account of the use of nylon mesh in the treatment of inguinal herniæ, has just arrived.

"The use of implants of foreign material," he says, "is almost as old as the history of operations for hernia . . . but most attempts have failed because of undesirable tissue reactions and sepsis." Surely there is only one type of tissue reaction to the introduction of any sterile foreign material into the human body—an aseptic inflammatory response that may or may not proceed to pus formation irrespective of actual infection introduced at the time of operation. Indeed, the essence of all operations of this type is the induction of just this type of response, with the production of a strong fibrous wall which, it is hoped, will take the place of the weakened muscles in the posterior inguinal wall.

Perhaps the greatest weakness of all "implant" operations, applied to indirect inguinal herniæ, is that they concentrate attention on the repair of the posterior inguinal wall, instead of on the re-creation of a functioning internal ring. But, as Ogilvie pointed out many years ago, in indirect herniæ the primary site of weakness is not the posterior wall but rather the stretched, weakened internal ring. Professor Stock does not say how many of his "ten patients with inguinal hernia" actually had indirect herniæ, but he implies that his operation may be used equally well for either direct or indirect. Surely there is a distinction to be made between the two.

He adds that "if the testis is abnormal or there is a thick hydrocele sac, orchidectomy is usually performed," which is a curious statement in this context. If an indirect hernia has reached such a stage that the internal ring and the posterior inguinal wall cannot be functionally re-formed, then the prospect has to be considered of complete closure of the canal, usually (though, as Aird points out, not necessarily) with orchidectomy. This, like all other forms of herniorrhaphy, does not guarantee against recurrence; and the patient, as well as the surgeon, must weigh the relative advantages which orchidectomy and complete closure of the canal offer. But in the treatment of hernia, it is the hernia that determines the necessity or otherwise of orchid-

2. Cockett, F. B., Elgan Jones, D. E. *Ibid*, 1953, i, 17.

ectomy, and not the state of the testis, let alone the state of the sac or tunica. To say that orchidectomy is usually done "if the testis is obviously abnormal" is surely irrelevant in this context: to say that it is usually done if "there is a thick hydrocele sac" is a little radical. When else would one do an orchidectomy for hydrocele?

Inexpensive, ubiquitous, malleable, and indestructible, nylon may be; and it is perhaps some comfort to know that when we have shuffled off our mortal soles the immortal uppers will still live on: but will they help my hernia?

Methodist Mission Hospital,
Ilesha, Nigeria. H. J. WRIGHT.

IDENTIFICATION OF DRUGS

SIR,—We are interested in the letter from Dr. King, in your issue of April 10.

This company manufactures its tablets with an identification mark, and we issue, on request, details showing which marks coincide with which drugs. Furthermore, in our advertisements in the medical press, we often show a picture of the actual tablet so that doctors may become familiar with the marking on the tablet. We know that some other manufacturers adopt somewhat similar policies.

Bayer Products Ltd.,
London, W.C.2. L. M. SPALTON
Director.

TREATMENT OF DEAFNESS

SIR,—In your issue of March 13, Mr. Robin warns the medical profession and its hard-of-hearing patients against "claims made for improved hearing by re-education methods."

It seems that he has, once again, confused the purely physical ability to hear with hearing in its broadest sense—namely, the ability of the cerebral cortex to interpret and respond to the auditory signals it receives from the ear in the course of daily hearing.

It is hard to say why Mr. Robin wishes to give your readers the impression that auditory training is said to improve the patient's physical ability to hear, when no such claim has been made. The very term implies that auditory re-education deals solely with cortical hearing. Obviously there is no simple, single, "scientific" test or measurement for a complex function which embraces a wide variety of auditory achievements such as recognition, discrimination, reaction-time, and memory for an endless variety of sounds received under dozens of different conditions, and which, in the hard-of-hearing, is further governed by fear, doubt, fatigue, lack of confidence, and even personality change.

Yet Mr. Robin demands that these aspects of hearing, and any change therein, be gauged by tests designed solely for gauging physical change in the peripheral auditory mechanism. Without such "scientific proof," he says, there can be no improvement in hearing, even though the patient's relations, associates, or employers state freely that it is very evident that the patient hears better. When confronted with such evidence, Mr. Robin mistakes cause for effect and seeks refuge in the suggestion that the patient's ability to "listen" has improved, even though we have painstakingly shown him that the improvement included sounds and conversations for which the patient could not possibly be listening.

As an aural surgeon, Mr. Robin must recall that the rather unscientific "social adequacy index" was adopted to assess hearing improvement in fenestrated cases, simply because pure tone and speech audiometry too often failed to portray the clinical results.

At this unit we assess improvement by what, in our opinion and long experience, is the most comprehensive way of depicting the results of auditory rehabilitation—the hearing disability questionnaire. This lists and indicates graphically the patient's stated ability before and after re-education for: conversation across a desk and a room, round a table, and in groups; speech and sounds other than speech (bells, buzzers, sounds from behind him, and from room to room); telephone, television, radio, confidential tones, whispered speech, and so on. Mr. Robin makes no mention of this in his letter. It might interest him to know, and to inquire why, the results of rehabilitation of the orthopædically handicapped are also assessed and recorded in such homely and "unscientific" terms as "turning over in bed," "combing and brushing the hair," "drinking from a glass," "walking up and down stairs," "striking a match," and so on.

The tone of his letter implies that auditory re-education is a worthless quackery whose "principle needs medical and scientific investigation before the practice is recognised as of true value," when in fact its use, both with and without hearing-aids, has long been practised in many of the most important auditory rehabilitation centres of the world.

Mr. Robin's motives are not to be questioned, but it is to be regretted that he has seen fit to voice his opinion publicly and dogmatically on the worth of a very specialised field of endeavour—after only a half-hour's exposure to it. In seeking to protect the hard-of-hearing public from being exploited, he has only succeeded in directing them away from the type of help they so sorely need. We trust that this letter will be able to undo the harm.

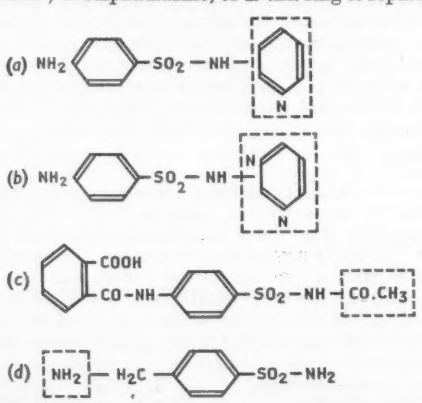
Ardente Audiotherapy Unit,
London, W.1. ELIZABETH CHADWICK.

CHEMICAL STRUCTURE OF SULPHONAMIDES AND THEIR EFFECT ON PERISTALSIS

SIR,—The effect of phthalylsulphacetamide on intestinal peristalsis was mentioned in your journal last year [1]; so I am writing to draw your attention to some experiments done in Germany. These have shown that the action of various sulphonamides on peristalsis is closely related to their structure.

Enders [2 3] and Kleibel [4 5] have found that certain groups of sulphonamides inhibit peristalsis, apart altogether from their antibacterial action in intestinal infections.

Sulphathiazole ('Cibazole,' 'Eleudron'), sulphapyridine ('Eubasine'), and phthalylsulphathiazole [6] ('Taleudron') inhibit peristalsis in experimental concentrations of about 1 : 2000, which should be attained with a dosage of 8–10 g. daily in the human subject. Their chemical structure shows a benzolsulphonamide group attached to a ring containing a single N-atom (fig., *a*). If benzolsulphonamide is combined in a molecule with a ring carrying a double N-atom (*b*), as in sulphapyrimidine ('Debenal') or sulphadiazine, or if this ring is replaced by



an aliphatic chain (*c*), as in sulphacetamide ('Albucid'), sulphaguanidine, and phthalylsulphacetamide, peristalsis is inhibited only at an experimental concentration of about 1 : 500, which would require a dosage of 36–40 g. daily in man. In other words, the quantity needed to inhibit peristalsis has to be four times as great.

1. *Lancet*, 1953, i, 831.
2. Enders, A. *Dtsch. med. Wschr.* 1951, **76**, 1404.
3. Enders, A. *Dtsch. Z. Verdau. Stoffwechselkr.* 1953, **13**, 236; *Arch. exp. Path.* 1943, **201**, 366.
4. Kleibel, F. *Dtsch. Z. Verdau. Stoffwechselkr.* 1952, **12**, 257.
5. Kleibel, F. *Ibid*, p. 183.
6. Henning, N. *In* von Bergmann, Frey, and Schwiegk's Handbuch der Inneren Medizin. Berlin, 1952; vol. III, part 2, p. 37.

Finally there is another sulphonamide, aminomethylbenzolsulphonamide (' Marfanil '), which has been shown both experimentally and clinically to excite peristalsis instead of inhibiting it. This preparation differs from those previously mentioned in having an NH_2 group joined to its benzole ring by a methyl group (*d*). It is interesting to note that it also differs from the others in its effect on intestinal bacteria.

These actions were demonstrated on the gut of rat and guineapig, and they did not persist longer than one hour. Desensitisation may thus be ruled out.

Medical Polyclinic,
Würzburg University. FRANZ KLEIBEL.

THE RECENT BURN

SIR,—Correspondents have lately discussed the desirability of leaving blisters intact when dealing with minor burns in industry. I have found that undiluted 1% electrolytic sodium hypochlorite solution, applied immediately in the form of a compress, prevents the formation of blisters; or if they have already formed on a recent burn, they are quickly reduced. Since the skin remains unbroken, there is absolutely no risk of infection with this method; moreover, it takes very little time, and pain is much reduced. If the skin is broken, the hypochlorite should be diluted to form an isotonic solution.

London, W.1. M. MARGARET DURRANT.

TREATMENT OF THYROTOXICOSIS WITH POTASSIUM PERCHLORATE

SIR,—We should be grateful if you would allow us to add a postscript to our article of April 10. We there described a patient whose gastric symptoms became much worse when her treatment was changed from methyl thiouracil (50 mg. daily) to potassium perchlorate (100 mg. daily). The dyspepsia disappeared when she was put back on methyl thiouracil, but reappeared a second time when potassium perchlorate was given. She was known to have a diaphragmatic hernia, and we concluded that perchlorate was probably irritating an already inflamed gastric mucosa.

Further experience with this patient makes this conclusion unlikely.

After another period on methyl thiouracil the gastric symptoms again increased, and became incapacitating. They mainly occurred when she went to bed at night, and consisted of severe epigastric pain and vomiting. These symptoms were only partially controlled by outpatient therapy and she was admitted to hospital. After a few days' treatment by posture, diet, and alkalis the symptoms rapidly subsided, and we took the opportunity of testing the effect of potassium perchlorate under controlled conditions.

For four consecutive 5-day periods she was given tablets of identical appearance, labelled A, B, C, and D, to be taken twice daily. Tablets A and C contained lactose only, tablets B and D contained 200 mg. of potassium perchlorate. The content of the tablets was not known to the patient, the nursing staff, or the clinical clerk who recorded the symptoms daily. During the 20-day test period only one attack of epigastric pain and vomiting occurred. This happened while she was taking tablet A (lactose). At the time of the test potassium perchlorate clearly did not irritate her gastric mucosa, although gastric symptoms had recently been present and the mucosa might be expected to be in a sensitive state. It seems probable that the exacerbations of dyspepsia twice observed in the past when she was taking potassium perchlorate were not caused by the drug.

This was the only case, out of 108, in which there seemed to be good evidence of gastric irritation by potassium perchlorate. Since further experience has shown that this evidence was probably misleading, it now seems unlikely that potassium perchlorate will prove to be a gastric irritant, although this possibility must still be kept in mind.

University College Hospital
Medical School, London. M. E. MORGANS
W. R. TROTTER.

METHYLPENTYNOL AS A HYPNOTIC FOR OLD PEOPLE

SIR,—Most elderly patients require some artificial aid to sleep, but the range of suitable hypnotics for routine use is very limited. The drugs commonly used include paraldehyde, chloral hydrate, sodium bromide, the traditional "Mist. Three-fifteens," and—most widely used of all—the barbiturates (mainly the "medium-acting" and "short-acting" ones). For old patients nearly all these hypnotics have some disadvantages.

I would like to report a trial of a comparatively new hypnotic drug, methylpentynol (' Oblivon '). Although its chemical structure bears superficial resemblances to paraldehyde and to methyl alcohol, methylpentynol is a separate drug in its own right. Methylpentynol (methylparafynol in U.S.A.) is a simple unsaturated aliphatic carbinol, 3-methyl-pentyne-ol-3, having the structural formula: $CH{:}C.C(CH_3)(OH).CH_2.CH_3$.

The literature on this drug has been reviewed [1] but, with the exception of a limited study of the drug in fifty-two psychiatric patients aged 61 and over,[2] the usefulness of methylpentynol as a mild hypnotic for the elderly has received little attention.

All the patients studied were aged 65 years or over. The report is based on a series of ninety-four patients, of whom thirty-two were aged 65–74, forty-three aged 75–84, and nineteen aged 85 or more. There were twenty-eight men and sixty-six women. All were general hospital patients and were under continuous observation, day and night. The great majority had required regular dosage with other commonly used hypnotics, with variable effect and for varying periods, up to the time of beginning methylpentynol treatment. Only those who received the drug continuously for a minimum period of 7 days or more were included in this study: thirty-eight patients received the drug nightly for 21 days or more, and twelve for 42 days or more. The minimum total dosage was 6·7 g., the maximum 144 g. The longest trial was in a man aged 76 who received a total of 144 g. over a continuous period of 72 days.

Method of Administration.—The unit dose of methylpentynol is 250 mg., and this was incorporated in one drachm of elixir specially prepared by the manufacturers. Any drug, if sufficiently soluble in water and not objectionable in taste, is more conveniently given to old people in liquid form rather than as tablets or capsules. The crude drug, methylpentynol, is a volatile liquid with a vile burning taste, far worse than paraldehyde, and it was therefore originally dispensed in capsules. For the purpose of this study, however, it was incorporated in an elixir, which disguised its taste. The most effective dose was 4–6 drachms (1·0–1·5 g.). Smaller doses seldom had a hypnotic effect, and larger doses had no added advantage. Altogether, forty-four patients received a dose of 4 drachms nightly for periods varying from 7 to 59 days; forty-eight were given a nightly dose of 6 drachms for periods of 7 to 49 days, and twelve were given a dose of 8 drachms nightly for periods ranging from 12 to 72 days.

Assessment of Efficiency.—The effectiveness of the drug on each individual was observed by doctors and by senior nurses, who also recorded every half-hour during the night whether or not the patient was asleep. Special charts were used and records were kept every night while the drug was being given. After the trial, the hypnotic effect for any night was noted as "good" if after the dose had been given the patient had been asleep within 1 hour, and had remained asleep for at least 5 hours. The response was noted as "poor" if sleep was broken, or had not ensued within 2 hours of giving the drug, regardless of the duration of sleep. In any particular patient, the drug was said to have been "efficient" if a "good" night's sleep was obtained on 70% or more of the nights on which it was given.

Results.—In sixty-one of the ninety-four patients (64%), the drug was found to be "efficient." Its prolonged use gave no troublesome side-effects, and there has been no evidence of addiction. When the hypnotic effects wear off, patients remain quietly sedated and do not become restless or noisy, so there is usually no need to repeat the dose during the

1. *Brit. med. J.* 1953, ii, 435.
2. May, P. R. A., Ebaugh, F. G. *J. Amer. med. Ass.* 1953, **152**, 801.

night, and excessive drowsiness next day is thereby avoided. The hypnotic action is a mild one, and the drug will not produce sleep in the presence of pain or acute mental disorder.

Thus, methylpentynol was found to be an efficient hypnotic in almost two-thirds of these patients. It appears to be a useful drug for elderly patients needing a mild hypnotic; and it is apparently safe and free from troublesome side-effects.

I should like to thank Dr. A. G. Anderson, Dr. A. W. Hendry, and Dr. W. R. Gauld for permission to include patients under their care in this investigation. I am also indebted to members of the nursing staff at Glenburn Wing, Woodend General Hospital, Aberdeen, for their willing coöperation. Methylpentynol elixir was supplied by British Schering Ltd.

Geriatric Unit,
Royal Infirmary,
Perth.

RONALD G. SIMPSON.

MOUTH-PIECE FOR USE WITH PNEUMOFLATOR IN RESPIRATORY PARALYSIS

SIR,—In your issue of Dec. 12 Dr. Beaver and Dr. Gilliatt described a cheap and simple improvisation of a mouth-piece for use with lung inflators. It was devised to take the place of the face-mask which is commonly used with these machines in maintaining artificial respiration. In this hospital we have had long experience in methods of artificial respiration, particularly for poliomyelitis, and we were fully aware of the difficulties encountered when using the face-mask in the conscious patient. Since the description of this mouth-piece was published, we have had the opportunity to give the mouth-piece (and modifications of it) an extensive trial in two intelligent adult patients. Both were loud in their praises for a device which they could accept with great comfort where previously, with face-masks, they were anxious, even alarmed, and almost certainly under-ventilated at times, even when the mask was being applied correctly.

Western Hospital,
Seagrave Road,
London, S.W.6.

W. HOWLETT KELLEHER.

NURSING BY THE MOTHER

SIR,—This correspondence has arisen out of the subject of cross-infection in hospitals, raised by the Pickerills in their article of Feb. 27; but I would like to add these comments in support of Dr. Lowenfeld's letter of April 10. She emphasises (1) the structure and organisation of the hospitals in which children are treated; (2) reconsideration of the training of nurses who will care for them and study of the ways in which help of the mother can be enlisted; (3) the value of play in recovery from illness. Homesickness and, above all, boredom work against recovery, and play is the only palliative.

There are many who agree that small children admitted to hospital should be accompanied by, and nursed as far as possible by, their mothers, but rather few, I fancy, who have found it easy to put into practice. This is where structure comes in. In most modern children's units and adapted old wards, the cubicles are too small to accommodate both mothers and children; the bathing and lavatory arrangements for the mothers are makeshift, and there is no sitting-room, dining-room, or telephone for them.

If it became known to the public that arrangements were adequate and that mothers were expected to go to hospital with their babies and keep in touch with home from this outpost, the neighbours would feel their obligation to step into the breach more binding than they do at present—in the south of England, at any rate.

Our nursing-staff difficulties are going to increase, not diminish, and although children usually get a better deal than adults when shortage is acute, the staffing of wards at night often reaches dangerously low limits.

On the second point—"Reconsideration of the Training of Nurses" (and doctors, I would add)—it is often felt, if not actually declared, by those who have charge of sick children in hospital that the parents of a child are not good for it. The child may be brought in in a dirty condition; the hair may have nits; a distressing emotional scene occurs at each visiting-time; or the feed the baby was having may be "a bit out" by ordinary calculations; and, as if any further proof were required that the parents are to blame the child under proper nursing gets well, gains weight, looks rested, and, above all, looks clean. Is it surprising that nurses and doctors see little to change in the time-honoured method of taking over completely from the mother? When we admit a child to hospital, mentally we nail a notice over its cot or on the door of its cubicle—Under New Management.

At present, nurses in training hardly notice the parents in the picture. They certainly cannot have an opportunity of seeing mother and child as one, and they are rather too young to have a serious interest in the mother's character and competence. Ward sisters, on the other hand, have to develop what may be called critical sympathy with the mothers, and some have a special gift for it.

The new orientation will make big demands on them in that it requires much further study and the sacrifice, to some extent, of the bond they would normally have with the child. Having seen it begin to work in a pædiatric unit (in spite of the structure being unsuitable), I am moved to write this letter.

Department of Pædiatrics,
Stoke Mandeville Hospital,
Aylesbury.

DERMOD MACCARTHY.

THE HOSPITAL MAKES FRIENDS

SIR,—The letter by "Registrar in Teaching Hospital" (April 10) illustrates the difficulty of conveying in writing a precise point of view. Writing as a psychiatrist, I assumed that, by the wording of my letter of March 10, it would be clear to your readers that I was not a general practitioner. I wonder whether it is not a common fault for people to interpret what they read in terms of their own problems.

At one clinic at which I worked before the late war, we had a weekly case-conference to which all concerned were invited. I feel this made for coöperation between the clinic and the general practitioner, as well as between other social services connected with the welfare of the patient.

Bishop's Stortford,
Hertfordshire.

D. N. HARDCASTLE.

A WORD WANTED

SIR,—With Dr. Apley's search for the best antonym to "retrospective" (April 10), I have that sympathy which comes from failure, partial or complete, in a similar quest. In my own attempt,[1] I finally settled for "prospective," not too happily, since this word has acquired connotations other than that desired. In my private vocabulary at the time, I used "Promethean" and "Epimethean" to make this contrast; and I just wonder if a transfer from upper to lower case might not supply Dr. Apley's needs, and those of others. The words "promethean" and "epimethean" are euphonious, they suit the desired meaning, and they have no taint of that hybrid origin which has kindled so much etymological flame.

Department of Medicine,
The Royal Infirmary, Manchester, 13.

D. A. K. BLACK.

SIR,—"Prespective" seems right. Præspective might be better, but we have "predestined" and "prescribed" and recently "pre-selective"; and American "pediatricians" would certainly omit the "a."

Bristol.

ALLAN MCFARLAN.

SIR,—Dr. Apley's difficulty seems to have been answered this very week by no less an authority on the

1. *Lancet*, 1953, i, 305.

use of words than Sir Winston Churchill. In a reply to Mr. Shinwell on a question concerning the atom bomb, he said: "I endeavour to allow my thoughts to play in retrospect as well as in prospect over all my acts."

Perhaps that too gives us a clue to the approach we should adopt to both forms of research.

Thornton Heath, Surrey. S. G. HAMILTON.

PATHOLOGISTS AND PNEUMOCONIOSIS

SIR,—I hate prolonging this already rather long correspondence any further, but I find Dr. Fletcher really hard to please.

Last time (March 20) he blamed the absence of a pathological classification for missed post-mortem diagnoses, and he dismissed the pathologists' approach to the problems involved for that reason. This time (April 3) he finds that the greatest source of sampling error in post-mortem statistics is the failure of all possible cases to reach the necropsy table.

As far as the intra-vitam certified cases are concerned, the necropsy is obligatory by law and the procedure is foolproof. As for the non-certified cases, the times when a coalminer would hesitate to mention his chest troubles for fear of losing his job are long gone. At present, it would mean a failure on the part of the coalminer, his dependants, his trade union, and—dare I mention it?—his doctor if the case is not fully investigated before or at least after death. The first two parties would be activated by the prospect of a pension and the other two by the wish to do their job; all that is required is a phone call to the coroner.

In these circumstances, while I agree that even this quadruple failure may happen as an occasional and deplorable occurrence, I feel it is rather hard of Dr. Fletcher to consider that it does so frequently. His statement implies a censure on G.P.s in colliery practices, and I doubt that they deserve it.

Dr. Fletcher mentions the concept of "pulmonary dust disease." I agree with him there, but, as long as the present Acts are based on a different definition, such considerations, valuable though they are, cannot form the basis of our actions.

Dr. Joules (March 27) tells me that at the necropsies of the 4500 fog victims in London in December, 1952, no fog was present in the lungs. While I have no wish to dispute this, I wish to point out that, according to the U.S. Government Report on the Donora fog disaster in 1948, sulphur compounds were found in the lungs of the victims at necropsy. So on that occasion at least, fog was present in the lungs.

Finally, in my original letter I asked for coöperation from other practitioners working in coalmining areas. I repeat my plea, for I feel that progress in the research into industrial dust disease will not come from recriminations and fault findings, but from coöperation and mutual assistance.

Abertillery, Monmouthshire. K. TRIGER.

CONTROL OF DENTAL CARIES

SIR,—I would like to add a few remarks about the control of dental caries, particularly since Dr. Burgess and Dr. Burton, in their article of April 10, discuss "Beginning at the Beginning." Although prevention does not apparently concern the G.P. directly, the principles of prevention are very much interwoven with many aspects of his work.

An excessive intake of carbohydrate is blamed for the production of caries, and I believe rightly so; but, in addition to the local effects, it may affect the "protein pool" of the body and incidentally the "organic turnover" of not only the teeth but other structures.

In the prevention of caries the introduction of one factor, say fluorine, may raise the level of resistance to a satisfactory height, but we do not know what it may do to resistance to other types of bacteriological invasion or equivalent forms of stress.

By aiming at calcium intake, have we pinpointed the mineral constituent, and by the recommendation of milk have we given an impression which overemphasises it as a "good food"?

Coming back to the carbohydrate intake, there are several factors involved: (*a*) the family feeding pattern; (*b*) the generally accepted habits of the circle in which we move; (*c*) the difficulty of restricting sweet consumption in one's own children without making them feel too different from their friends; (*d*) the feeding difficulties of early life and the easing of tension when sweeter foods are given because "after all a child as active as that must have something to keep going"; (*f*) an understanding of diet, especially from the point of view of breaking the habits produced by temporary stresses. Finally, the conversion of "dietetic hyperinsulinism" and its cravings to a normal metabolic pattern is probably not the least of the problems.

These remarks are not levelled in criticism; I am merely trying to show, if possible, how wide the problem of dental caries is.

Clapham, Yorkshire. J. A. FARRER.

SAFER HYPOTENSION

SIR,—Much interest has been focused in recent months not only on the advantages but on the dangers of the use of hypotensive techniques in surgery.[1–3] With the methonium compounds the degree and duration of the blood-pressure falls are often variable and not always easily reversed. It would seem from reports on the use of 'Arfonad'[4,5] that, because of its short action, this agent makes the use of hypotension a more controllable and hence a safer procedure. In our opinion, and that of others,[1] the safety of this technique can be further increased by combining it with hypothermia, thereby lowering the metabolism and oxygen requirements of the brain.

We have used the combination of hypothermia and hypotension (with arfonad) in a small series of selected neurosurgical procedures, and the results have been very satisfactory. These were operations for aneurysms and vascular tumours which would have proved difficult, if not impossible, with orthodox methods of anæsthesia. Hypothermia, and the drugs used in its production, will lower the systolic blood-pressure to about 100 mm. Hg, this fall being reinforced when required by the use of arfonad.

Hypothermia is produced by surface cooling using a modification of a technique already described.[6] All adult patients are given 50 mg. of chlorpromazine by deep intramuscular injection about one hour before anæsthesia is induced. This is combined with pethidine and/or promethazine, depending on the degree of consciousness. On arrival in the anæsthetic room, patients are prepared for operation in the usual manner, very small doses of thiopentone being required. Surface cooling with ice bags is then commenced, and any tendency to vasoconstriction, as shown by a sharp fall in skin-temperature, is overcome by the intravenous administration of further doses of chlorpromazine. The largest dose of this drug that we have used to date is 95 mg.

The light anæsthesia maintained with nitrous oxide-oxygen, together with the chlorpromazine, with or without trichlorethylene, has completely eliminated shivering. With this technique it has always been possible to reduce the rectal temperature to 32°C (89·6°F) within one hour of the first application of ice. All active cooling is then stopped and the temperature falls slowly during the operation to about 30°C (86°F).

1. See *Brit. med. J.* Feb. 6, 1954, p. 324.
2. Davison, M. H. A. *Anæsthesia*, 1953, 8, 255.
3. See *Ibid*, p. 263.
4. Anderson, S., McKissock, W. *Lancet*, 1953, ii, 754.
5. Kilduff, C. J. *Ibid*, Feb. 13, 1954, p. 337; Scurr, C. F., Wyman, J. B. *Ibid*, p. 338.
6. Dundee, J. W., Gray, T. C., Mesham, P. R., Scott, W. E. B. *Brit. med. J.* 1953, ii, 1237.

The arfonad is given by continuous infusion of a 0·1% solution, similar to the method of Scurr and Wyman.[5] A very slight head-up tilt (5°–10°) is used during operation.

The outstanding difference between this technique and those previously described is the small amounts of arfonad required to reduce the systolic blood-pressure to 60 to 70 mm. Hg. A drip rate of 5 to 10 per minute is rarely exceeded, 100 to 150 mg. of arfonad being the usual requirements for 3 to 4 hour operations. In one case a "pressure floor" of 70 mm. Hg systolic could not be passed by increasing the drip rate, and this only delayed the recovery. Tachycardia has not been observed in any case, presumably because of the hypothermia.

It is our aim to return the systolic blood-pressure to 90 to 100 mm. Hg before closure of the dura mater, and in this we have always succeeded. A rise of 15–20 mm. Hg occurred within 5 to 10 minutes of stopping the arfonad. Irrespective of the degree of bleeding, a bottle of blood or 'Intradex' is given quickly at this stage, resulting in a similar rise in the pressure. In the one instance where these measures were not sufficient, a 1 : 1,000,000 *l*-noradrenaline drip quickly rectified matters, and it was discontinued after 20 minutes.

No active attempts are made to restore the normal body-temperature at the end of the operation, and temperatures of 35°–37°C are attained within 6 to 8 hours, with a gradual return of normal blood-pressure.

Reduction in bleeding resulting from controlled hypotension has opened up new fields in the realms of plastic, E.N.T., and neurosurgery. In every case, however, one has to weigh the dangers of severe bleeding at operation and those which may result from the prolonged period of low blood-pressure. We feel that while arfonad is probably the greatest advance that has been made since the technique was introduced, its combination with hypothermia should rob controlled hypotension of many of its undesirable sequelæ.

Department of Anæsthesia, University of Liverpool. JOHN W. DUNDEE.
ITHEL LL. FRANCIS
Regional Neurosurgical Unit, Liverpool. C. B. SEDZIMIR.

SHOE DESIGN AND THE GREAT TOE

SIR,—May I, an outsider, join your discussion of shoe design?

I take the view that the normal environment of the foot is unshod on a yielding and uneven surface (sand, earth, &c.), so I have designed a shoe that will simulate this environment as closely as possible. First, a plaster impression of the foot is taken, with the foot bearing no weight but in a weight-bearing attitude, and from this a plaster model is made. The shoe is moulded directly on this model, the hypothesis being that the foot should design the shoe, not that the shoe should design and deform the foot.

The outside of the shoe is made of soft leather with a flexible rubber sole. The inside will fit every curve of the dorsum and the plantar surface of the foot. The insole will be rounded at the heel and metatarsal area, built up to the long arch, and even built up under the toes to aid them in their grasping action and also prevent the foot from sliding forward.

In the moulded shoe the entire plantar surface of the foot will help carry the body-weight: heel, long arch, five metatarsal heads, five toes, and even the webbed areas under the toes.

In the conventional woman's shoe the body-weight is carried by the base of the heel and the second, third, and fourth metatarsal heads. Because of the pointed shoe, the great toe is forced medially during walking, causing all the weight to be carried on the middle metatarsal heads with the subsequent formation of corns and callosities and deformities of the toes—the most serious of which is hallux valgus. In men, where the shoe is wider, but not wide enough, the most common condition is the callosity under the first and fifth metatarsal heads.

I have observed excellent results with shoes made in this way. Corns and callosities have completely disappeared within six to eight weeks. Within a year after wearing the shoes, many toe deformities begin to correct themselves; but it is too early to say what will happen to chronic deformities. At all events, pain is relieved immediately.

Philadelphia, U.S.A. H. T. LOVITZ.

SIR,—I was interested to read in your issue of March 27 a letter from Dr. Haines and Mr. McDougall. But I must disagree with their statement that, although flat shoes have become popular since the war, "they seldom appear in fashion magazines." My own company, in common with other leading manufacturers of flat shoes, publicise them extensively in fashion magazines and women's magazines. We also find that the fashion magazines often discuss our flat shoes in their editorial columns.

Selby Shoes Limited, London, W.1. J. F. H. HINTON.

AUTOHÆMOTHERAPY IN HERPES ZOSTER

SIR,—Two leading textbooks say of herpes zoster:

"The course of the eruption is uninfluenced by treatment." [1]

"Nothing will check the disease." [2]

Yet this is a severe affliction, which causes long-lasting neuritis and pain in the affected part, and, if it attacks the cornea, the result may even be loss of the eye.

In the past forty years I have treated many cases of herpes zoster by intramuscular injection of the patient's own blood, and when this treatment has been started in the first two days it has always checked the disease. The most dramatic improvement has been in herpes of the eye, and I believe that I have saved many eyes.

Using a 5-ml. syringe, 5 ml. of blood is withdrawn from a vein in the bend of the elbow and is injected into the deltoid muscle of the same arm. It is as well to repeat this injection of the patient's own blood the next day. Of course, in addition, the pain-relieving remedies should be used—i.e., aspirin, phenacetin, codeine, or pethidine—and an aperient should be used to counteract the constipation they cause.

This autohæmotherapy is simple and without risk. It should be given as soon as the illness is recognised. Unfortunately it is not much good three weeks later when the neuralgic pains cause so much distress.

London, W.1. V. NESFIELD.

3-D. IN MEDICAL ILLUSTRATION

SIR,—In your issue of April 10, you note (p. 787) an article of Dr. J. G. Robson and myself which appeared in *Anæsthesia* and which was illustrated by stereoscopic anaglyphs.

In his editorial comment the editor of *Anæsthesia* expressed the belief that "it is the first time that this type of stereogram has been used in a medical journal." In this comment he may strictly be correct, since I believe that there are several processes for producing these stereograms, though the final result of them all appears rather similar. Your note is a little more general however, and I think it would be unfair if your readers gained the impression that this is the first occasion on which stereograms by any anaglyphic procedure had appeared in a medical journal, because in a supplement to the November, 1953, issue of *Medicine Illustrated* there appeared some anaglyphs by Mr. P. Hennessy and Mr. J. Hardman.

This sort of confusion readily arises when a technique is new, and I apologise for occupying your space with

1. Conybeare, J., Mann, W. N. Textbook of Medicine. Edinburgh, 1952.
2. Taylor's Practice of Medicine. London, 1936; p. 1000.

a rather minor matter. It would, however, be a pity, through misunderstanding, to cause irritation to those concerned.

Department of Anæsthetics,
The Medical School,
Newcastle upon Tyne. E. A. PASK.

BILIGRAFIN IN CHOLECYSTOGRAPHY

SIR,—I have read the annotation on 'Biligrafin' in your issue of April 17 with interest. I am at present working with samples of biligrafin kindly supplied by Messrs. Schering A.G. of Berlin.

I have found the substance entirely satisfactory, fulfilling all the claims mentioned in your annotation, save that I now have to record a severe reaction. This occurred in an apparently healthy man of 72 years, suffering only from suspected gall-bladder disease and not at that time jaundiced.

The injection of biligrafin was slowly given intravenously. After 30 ml. had been injected the patient complained of a pricking sensation in the anus, and injection was immediately discontinued. Four minutes later, he suddenly lost consciousness. He was pulseless with stertorous breathing, pallid complexion, cyanosis of the extremities, and an imperceptible radial pulse. There was urinary incontinence. Resuscitation was achieved with the aid of continuous oxygen, injections of nikethamide ('Coramine'), antazoline ('Antistin'), and adrenaline. After 15 minutes, the patient regained consciousness and his subsequent recovery was uneventful.

One previous case of collapse is quoted by Hornykiewytsch and Stender [1] but no details are given.

Cambridge. M. W. P. WARD.

THE BOMBS

SIR,—Many people will be grateful for your leading article last week. The established facts about the bomb reduce to tragic absurdity the arguments of statesmen and military leaders that the world must, to preserve peace, devote itself to preparing for war. Homicide on a scale approaching this has hitherto been possible only when millions of people have been persuaded that their duty or interest lay in supporting war, and the act of war demanded that these millions should throw themselves into movement. The hydrogen bomb makes it possible, for the first time in the history of the world, for a few men in positions of power to dispense with the consent and active support of their people in waging war. Neither fear of retaliation nor any moral considerations will restrain the desperate. Indeed, the decision to use the first atom bomb appeared to many people then, and to far more since, to have no moral justification.

You praise our profession for the part some members of it have played in urging upon the world the paramount need for humanity to outlaw the mass murder which is at present condoned in war. Professor Haddow, to whose courageous letter in the *Times* you call attention, has suggested that scientists all over the world, profiting by the international status of science, should meet to appraise the human situation created by the existence of the hydrogen bomb, and set themselves to devise policies to prevent its manufacture. This is obviously a proposal of great value and I suggest that all of us have a duty to obtain for it the support of our professional organisations.

I should like to remind my colleagues that there is an organisation of doctors in this country which exists to study this great dilemma—namely, the Medical Association for Prevention of War. Under the auspices of this association, Prof. C. F. Powell, F.R.S., and Dr. Comfort will be addressing a meeting on the hydrogen bomb at at Friends' House, Euston Road, London, N.W.1, at 7.30 p.m. on Wednesday, April 28.

Bickley, Kent. DUNCAN LEYS.

1. Hornykiewytsch, T., Stender, H. S. *Fortschr. Röntgenstr.* 1953, **79**, 293.

SIR,—There is one aspect of the hydrogen bomb which few medical men will fail to recognise—it is the mental patient's weapon *par excellence*. Atomic research in the United States (we cannot speak for Russia, which keeps its own counsel) has long since passed from the sphere of weapon research into that of abnormal psychology. In such a context, it is hard to place confidence in the consideration that no sane authority will destroy itself. The sane man may say "If that man hits me I will hit him": the sane but cruel man, "If that man hits me, I will kill him and his whole family." But there is a recognisable and pathognomonic ring about the proposition "If that man hits me, I will burn down the house and kill us both." It leads naturally on to the further proposition "That man is going to hit me: I will burn down the house and kill us both to forestall him." To say that the policy of "massive retaliation" already exemplifies this state of mind is a medical, not a political, judgment—to those who remember the utterances which came from a certain burning Chancellery, the cravings for *Götterdämmerung*, for the deliberate mistake, for the opportunity to smash everything, are dangerous and present realities in both medicine and politics.

The paranoia of nations, being shared out, as it were, between a large number of normal, and a few abnormal, but directing, individuals is always diluted with normality, with some humane responses to which we can appeal. In both the major atomic powers today, it is largely so diluted. From the psychological standpoint, the traditional rigidity of Russia seems less menacing today, and in the context of this weapon, than the traditional hysteria of the United States. Both powers are subject to the pressure of world public opinion. I believe that a forthright and total renunciation of such weapons by our own country would have great psychotherapeutic value; it might help us to avoid the paralysis of public attitudes by guilt-feelings over the last atom bombs, which has affected the United States, and it would enormously raise our domestic morale and our external moral authority. This is a case where British opinion might without arrogance act as therapist. In spite of the propaganda of malicious people, we have no great fear or hatred of either side. We have few McCarthys or Berias to handicap us. The responsibility of reconciliation is one which we can all accept, and which the medical profession should be proud to lead. It is our only hope, after all, of surviving the century.

Loughton, Essex. ALEX COMFORT.

Parliament

Fewer Dentures

IN the House of Commons on April 15, replying to Mr. R. E. Winterbottom who raised the question of the number of dental technicians, Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said that the Ministry believed there were more of these workers than there was work for them to do. In 1948, 437 people applied for apprenticeships, and in 1949, 1205 people applied. In 1950, when many of these apprentices were not yet trained, 5 million dentures were supplied under the National Health Service. But in 1953 only 2 million dentures were supplied, and she thought that this figure would be the average annual demand for some years. If the service was a success fewer, and not more, technicians would be needed for people would look after their teeth and keep them longer. In the last quarter of 1953, 380,000 dentures were supplied; in the first quarter of 1954, 394,000. The effect of the treatment charges had been a vast increase in conservative work, particularly among children and adolescents. There was no desire to cheesepare on this service, but the Minister was convinced that there were enough technicians to deal with the situation. There

were between 200 and 250 technicians employed in the hospitals, and all except about 80 were in the teaching hospitals. At present the Whitley Council was drawing up an apprenticeship scheme for the training provided in hospital and local-authority laboratories.

QUESTION TIME

Hospital Consultants

Mr. A. A. H. MARLOWE asked the Chancellor of the Exchequer what consultations had taken place between the Treasury and the Ministry of Health on the expenses of hospital consultants employed in the National Health Service which were not deductible for income-tax.—Mr. J. A. BOYD-CARPENTER, financial secretary to the Treasury, replied: Hospital consultants are, like other employees, assessable under schedule E, and the same rules for expenses apply to them as to other taxpayers. I see no reason to propose legislation giving them preferential treatment. The general question of what expenses are admissible to such taxpayers is within the terms of reference of the Royal Commission.

Replying to a question, Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said that the number of consultants employed by regional boards in England and Wales who had transferred from whole-time to part-time service was 42 in 1951, 61 in 1952, and 46 in 1953.

N.H.S. Charges

Replying to questions, Miss HORNSBY-SMITH said that N.H.S. charges were introduced in 1952. The number of prescriptions dispensed by chemists in February, 1954, was 19,203,000, compared with 21,645,000 in February, 1953. The estimated cost to the Exchequer of dental treatment for these months was £1 million and £800,000 respectively.

Hydrocortisone Supplies

Replying to a question, Miss HORNSBY-SMITH said that production of hydrocortisone in this country started only recently. The supplies now available to hospitals receiving cortisone would be increased as the need arises.

Welfare Food Service

Replying to a question, Major GWILYM LLOYD GEORGE, Minister of Food, said that about 97% of those entitled to obtain milk or 'National Dried Milk' under the welfare foods service did so. The quantities of the vitamin supplements taken up in 1953 expressed as a proportion of the full entitlement were as follows: orange juice 29·4%; cod-liver oil 23·8%; vitamin tablets 32·6%. The percentage of persons who obtained the vitamin supplements was higher than these figures suggested, because many did not take their full entitlement.

Contamination of Citrus Fruits by Thiourea

Mr. JOHN PARKER asked the Minister of Food what action was being taken to safeguard the public from thiourea poisoning in oranges imported from Spain. Major GWILYM LLOYD GEORGE replied: Local authorities in whose areas such oranges have been reported have been approached with a view to their taking appropriate action. As a result they have warned merchants against further importation. The Spanish authorities have also warned all their fruit-inspection offices that the complete prohibition of the export of such oranges to Great Britain must be strictly enforced.

Public Health

Poliomyelitis in Denmark

Denmark had a formidable outbreak of poliomyelitis in 1952, when the attack-rate of the paralytic form in Copenhagen was 106 per 100,000 population. Hamtoft [1] has now compared the experience in 1953 with that in the preceding year.[2]

The epidemic of 1953 was surpassed only by those of 1952, 1944, and 1934. Between the outbreaks of 1952 and 1953 notifications fell to the lowest level about May 1,

POLIOMYELITIS IN DENMARK, 1952 AND 1953

Area	January, 1952, to April, 1953				May, 1953, to December, 1953				1952 + 1953: paralytic cases per 100,000 population
	Paralytic cases		Non-paralytic cases		Paralytic cases		Non-paralytic cases		
	Total	Per 100,000 population	Total	Per 100,000 population	Total	Per 100,000 population	Total	Per 100,000 population	
Copenhagen, metropolitan area ..	1289	106	1631	134	53	4	147	12	110
Rest of country ..	1271	41	1694	55	521	17	672	21	58
Total Denmark ..	2560	58	3325	76	574	13	819	19	71

and for the purpose of assessing the two outbreaks this date is taken as the dividing-point. The most striking difference between the two epidemics is in the relative distribution of cases between Copenhagen and the rest of the country, shown in the accompanying table. Whereas in 1952–53 the attack-rate of paralytic poliomyelitis was nearly three times greater in Copenhagen than in the rest of the country, in May to December, 1953, the rate in Copenhagen was only a quarter of that in the rest of the country. Furthermore, "The counties which showed the greatest number of cases in 1952 practically escaped the epidemic in 1953, while the counties not stricken by the epidemic in 1952 showed large numbers of cases in 1953."

1. Hamtoft, H. *Dan. med. Bull.* 1954, 1, 12.
2. See *Lancet*, 1953, ii, 196.

England and Wales in 1953

The Registrar-General publishes this week further details [3] for England and Wales in 1953; he had already given some provisional figures in an earlier return.[4] The estimated home population of England and Wales at Dec. 31 was 44,166,000—an increase of about 420,000 since the census in April, 1951. On the basis of the death-rates for 1952, it is reckoned that the expectation of life of a boy at birth is now 67·06 years and of a girl 72·35 years. On the basis of the death-rates for the years 1901–10, the expectations were 48·53 and 52·38 respectively. In an analysis of the causes of death, it is noted that the number of deaths from accidental poisoning continues to rise, reaching 659 in the first nine months of 1953, compared with 586 during the corresponding nine months of 1952. The number of suicides increased in the same period from 3299 to 3541. A comparison of death-rates of children under one year of age in the September quarter of 1953 shows that the rate of 22 per 1000 related live births compared with the following rates in other countries: Netherlands 19, Australia 25, U.S.A. 26, Scotland 28, France 33, Italy 64.

The School Lavatory

In his 1953 report to the City of Oxford Education Committee, Dr. J. F. Warin comments on the continuing failure of some of the schools to remedy obvious defects in sanitary arrangements. Provision of bolts on lavatory doors, lavatory chains, and brackets for toilet-paper and a supply of paper, cost little and are too often lacking. "The key personnel in this matter are the head teacher and the caretaker." Dr. Warin again emphasises the need for schools to play their part in training children in cleanly habits—for which a sufficiency of properly equipped lavatories (with wash-basins) is essential. "The experience of most head teachers has been that provided conveniences are kept in good order and supplied with toilet paper on proper brackets then care is exercised by the children."

3. The Registrar-General's Quarterly Return for England and Wales. Quarter ended Dec. 31, 1953. H.M. Stationery Office. Pp. 32. 2s.
4. See *Lancet*, Jan. 30, 1954, p. 260.

Notes and News

A CANADIAN COLLEGE OF GENERAL PRACTICE

LAST year, at a meeting of the Canadian Medical Association, it was decided to set up a college of general practice "within Canadian organised medicine" with the following aims:

To establish an academic body with broad educational aims.
To arrange for undergraduate teaching by and for general practitioners.
To arrange for the presentation of postgraduate education for general practitioners.
To arrange for research in general practice.
To arrange for publication of original articles by general practitioners.
To arrange for hospital staff appointments for general practitioners.
To provide suitable recognition to members in the field of general practice.
To do all things necessary to maintain a high standard in general practice.

The college will be officially inaugurated at the meeting of the association at Vancouver in June. Applications for membership should be sent to the College of General Practice of Canada, 244, St. George Street, Toronto 5, Ontario.

DANISH BULLETIN

Denmark, with just over four million inhabitants, makes a contribution to medical knowledge out of proportion to its size; but, since the Danish language is understood by less than 1% of the people of the world, the extent of this contribution may not always be apparent. Accordingly a new monthly bulletin in English,[1] sponsored by the Danish Medical Association, medical schools, and national health service, should prove especially valuable. Its purpose is to survey Danish medicine by means of original articles, short communications, and annotations; and an article in the first issue is referred to in our public-health section this week. The bulletin will be sent without charge to subscribers to *Ugeskrift for Læger* and, on request, to medical institutions.

RENÉ SAND MEMORIAL

THE International Conference of Social Work is opening a memorial fund to commemorate the life and work of Prof. René Sand, its founder, who died in 1953.

Professor Sand, who held the chair of social medicine in the Free University of Brussels, was a former secretary-general of the League of Red Cross Societies, and had also shared in the foundation of the World Health Organisation. He was at the time of his death president of the International Hospital Federation.

It is proposed that the memorial fund shall be used to award a biennial prize for "outstanding service in social welfare or social medicine." Contributions may be sent to Mr. G. E. Haynes, the president of the conference, 26, Bedford Square, London, W.C.1, or to the secretaries of the national committees of the conference.

THE UNMARRIED MOTHER

A PAMPHLET by a Roman Catholic social worker[2] gives a brief but comprehensive survey of the social and moral causes of illegitimacy and the measures for prevention and alleviation of the suffering caused to women and their illegitimate babies. Written from the Roman Catholic viewpoint, its approach is sensible and practical, and due tribute is given to the work of other bodies.

University of London

On March 19 the Graham medal was presented to Prof. G. R. Cameron, F.R.S.

University of Glasgow

On June 16 the honorary degree of LL.D. will be conferred on Prof. J. H. Dible, Sir John McNee, and Prof. G. I. Strachan.

Royal College of Physicians of London

Dr. J. Forest Smith will deliver the Croonian lectures on Tuesdays, May 4 and 11, at the college, Pall Mall East, S.W.1, at 5 P.M. His subject will be Nutrition and Child Health.

1. Danish Medical Bulletin. Subscription £1, $3, or equivalent; payable to Ejnar Munksgaard, 6, Nørregade, Copenhagen.
2. The Unmarried Mother and her Child, by MARY WALSH. Catholic Truth Society, 38, Eccleston Square, London, S.W.1. Pp. 21. 4*d*.

National University of Ireland

Mr. Patrick FitzGerald has been appointed associate professor of surgery at University College, Dublin. Dr. Paul Cannon has been appointed professor of physiology, and Dr. Fergus O'Rourke professor of zoology, at University College, Cork.

The degree of M.D. has been awarded to A. P. Barry.

Royal College of Obstetricians and Gynæcologists

On Friday, May 21, at 5 P.M., at the college, 58, Queen Anne Street, London, W.1, Mr. Ian Donald will deliver the Blair-Bell lecture. He is to speak on Atelectasis Neonatorum.

Institute of Dermatology

Two semi-permanent exhibitions are being shown at the institute during the summer course. The first, from May 3 to 22, by Dr. J. O. Oliver, will be on Animal Parasites in Diseases of the Skin.

Royal Sanitary Institute

The annual health congress of this institute is to be held at Scarborough from April 27 to 30, under the presidency of the Earl of Feversham.

Diabetic Association

The scientific meeting of this association will be held at University College Hospital Medical School, Gower Street, London, W.C.1, on July 16 and 17. On July 16, at 2.30 P.M., Dr. K. Hallas-Møller will deliver the Banting lecture, on the New Insulins. Those who wish to read communications should write to the association, 152, Harley Street, London, W.1.

Where to Practise

The Medical Practices Committee have revised the classifications of areas for England and Wales. A doctor who is proposing to enter practice should apply for up-to-date information from the executive council of the district before taking steps to secure surgery and waiting-room accommodation.

Medical Art Society

This society is holding an exhibition at Walker's Galleries 118, New Bond Street, London, W.1. Until May 8 it will be open from 10 A.M. to 5 P.M. (Saturdays 10 A.M. to 1 P.M.).

Association of Social Workers

This association is holding a course at County Hall, Westminster Bridge, London, S.E.1, on May 28, and 29, on the Social Worker and the Group Approach. The first session will take place at 6 P.M. on Friday, the 28th. Further particulars may be had from the conference secretary, Silverbeck, Stanwell Moor, Middlesex.

National Society of Children's Nurseries

A conference on the Needs of the Family in a Changing Society is to be held on Friday, May 7, at 10.30 A.M., at County Hall, Westminster Bridge, London, S.E.1. The speakers will include Prof. Fraser Brockington, Dr. Alice Stewart, and Dr. D. W. Winnicott. Further particulars may be had from the secretary of the N.S.C.N., 45, Russell Square, W.C.1.

Prizes for Clinical Research

A year ago the South West Metropolitan Regional Hospital Board decided to offer prizes to encourage "minor items of clinical research" (see *Lancet*, 1953, i, 249). The following awards for 1953 have been announced:

Up to 3 prizes of £100 each for consultants and S.H.M.O.s.—Dr. M. Hamilton, formerly psychiatrist (S.H.M.O.), Springfield Hospital (treatment of paranoid psychoses); Dr. A. M. Read, assistant chest physician, Portsmouth chest clinic (ventilatory defect following treatment by artificial pneumothorax); Dr. D. A. J. Williamson, consultant pædiatrician, Southampton, Winchester, and Treloar groups (epidemiological and clinical survey of ascariasis).

Up to 3 prizes of £100 each for senior registrars, registrars, etc.—Mr. G. Bennett, D.O.M.S., senior registrar, Southampton Eye Hospital (ætiology and surgical treatment of glaucoma); Dr. G. S. Crockett, senior medical registrar, Lambeth Hospital (measurement of pulse-wave velocity in the human subject); Dr. C. Donovan, formerly psychiatric registrar, St. James' Hospital, Portsmouth (plasma-ascorbic-acid response in psychotics).

Up to 3 prizes of £100 each for house-officers.—Mr. A. O. Wilson, F.R.C.S., formerly house-surgeon, Royal Hants County Hospital (absence of fluid and electrolyte disturbances in patients undergoing partial gastrectomy and given limited amounts of fluid intravenously after operation); Mr. M. Wynyard, F.R.C.S., formerly house-surgeon, St. James' Hospital, Balham (anatomy of the big toe with regard to the long saphenous nerve).

A similar competition is being held this year and particulars will be sent to group medical committees in the region.

Medical Association for the Prevention of War

In collaboration with Science for Peace, this association has arranged a meeting on the Hydrogen Bomb. This will be held on Wednesday, April 28, at 7.30 p.m. at Friends' House, Euston Road, N.W.1, and the speakers will be Prof. C. F. Powell, F.R.S., of Bristol, and Dr. Alex Comfort. The address of the association is 291, Burntwood Lane, S.W.17.

Davidson Clinic, Edinburgh

A summer school on Conscience and Psychology is to be held at the clinic, 58, Dalkeith Road, Edinburgh, 9, from July 28 to Aug. 3.

Research Board for the Correlation of Medical Science and Physical Education

This board has given the William Hyde award (£300) for 1952 to Miss P. C. Colson, the general secretary to the Central Council of Physical Recreation.

Sister Kenny's Contribution to the Treatment of Poliomyelitis

Dr. M. E. Knapp, of the Elizabeth Kenny Institute, Minneapolis, will speak on this subject at Queen Mary's Hospital for Children, Carshalton, on Monday, May 10, at 5 P.M. Further particulars will be found in our advertisement columns.

Institute of Hospital Administrators

The annual conference of this institute is to be held from May 6 to 8 at Oxford. The subjects chosen for discussion are: The Patient as the Centre of the Hospital; Coöperation with other Services in Treating the Patient; and Patients' Complaints and Criticisms. Further particulars may be had from the secretary of the institute, 75, Portland Place, London, W.1.

French Documentary Film on Cancer

Sir Stanford Cade will introduce this film when it is shown at the Institut Français, 15, Queensberry Place, London, S.W.7, on Wednesday, May 12, at 8 P.M.

The film was made by Etudes Cinématographiques, under the direction of Dr. Pierre Thevenard of the Institut Pasteur, as part of the anti-cancer campaign. The 13 sections include cartoons, laboratory work with animals, acted scenes, and interviews with successfully treated patients. Tickets may be had from the scientific office of the French Embassy, 22, Wilton Crescent, S.W.1.

Association Internationale pour l'Étude des Bronches

The fourth congress of this association will be held at Geneva on June 5 and 6, under the presidency of Prof. André Montandon. The subjects chosen for discussion are: Blood-supply of the Bronchi, Classification of Bronchial Adenomas, and Surgical Treatment of Bronchial Dilatation. Further particulars may be had from the secretary of the congress, Clinique Universitaire d'Oto-Rhino-Laryngologie, Hôpital Cantonal, Geneva, Switzerland.

Human Milk Bureau.—With the help of Queen Charlotte's Maternity Hospital, London, Camera Talks (23, Denmark Place, W.C.2) have produced a filmstrip illustrating the work of the hospital's milk bureau.

Appointments

FIELD, C. M. B., M.D. Belf., M.R.C.P., D.C.H.: consultant pædiatrician, South Belfast H.M.C.

KLEIN, DOROTHY, M.B. Edin., D.OBST.: asst. M.O., Southend-on-Sea.

RICHARDSON, J. D., M.D. Lond., D.P.M.: consultant children's psychiatrist, South Lincolnshire.

ROONEY, JEAN F. W., M.B. Dubl., D.C.H.: asst. school M.O., Bedale & Northallerton area.

SEWELL, T. P., M.D. Manc., D.P.H.: deputy county M.O.H. and deputy school M.O., Lancashire.

WATSON, JEAN M. I., M.B. Leeds, D.OBST.: asst. maternity and child welfare M.O. and school M.O., Derbyshire.

WESTON, J. W., M.R.C.S., D.T.M.&H.: asst. pathologist (S.H.M.O.), Halifax hospitals group.

YOUNG, R. J., M.D. Belf., M.R.C.P.: consultant pædiatrician, Londonderry and north west area of Northern Ireland.

Sheffield Regional Hospital Board:

BATES, T. J. N., B.A., M.B. Dubl., D.P.M.: senior asst. psychiatrist, Saxondale Hospital, Radcliffe-on-Trent.

CONN, HERBERT, M.D. Berlin: senior asst. psychiatrist, Kingsway Hospital, Derby.

LUMLEY, W. T. C., M.B. Lond., D.O.M.S.: asst. ophthalmologist, Chesterfield Royal Hospital and associated school ophthalmic clinics.

MONYPENNY, ISABELLE G., M.R.C.S., F.F.A. R.C.S., D.A.: consultant anæsthetist, Sheffield R.H.B. and United Sheffield hospitals.

OSTROWSKI, T. M., M.B. Polish School of Medicine, Edinburgh: senior casualty officer, Beckett Hospital, Barnsley.

Diary of the Week

APRIL 25 TO MAY 1

Monday, 26th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Section of Odontology.* Mr. R. L. Hartles, B.SC.: Carbohydrate Degradation in the Mouth.

HUNTERIAN SOCIETY
7.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Mr. W. R. Le Fanu, M.A.: Hunter-Baillie Manuscripts.

MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *Section of General Practice.* Dr. W. E. C. Thomas: Obstetrics in General Practice.

Tuesday, 27th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Section of Medicine.* Prof. Max Rosenheim, Dr. S. J. de Navasquez, Dr. J. M. Stansfeld: Chronic Pyelonephritis.

ROYAL STATISTICAL SOCIETY
6 P.M. (Westminster Medical School, Horseferry Road, S.W.1.) *Study Circle on Medical Statistics.* Discussion of Working Party Report on Assessment of Need for Clinical Services.

SOCIETY FOR ENDOCRINOLOGY
5.15 P.M. (1, Wimpole Street, W.1.) Dr. Gregory Pincus: Pathways of Steroid Synthesis in Animal Organism.

Wednesday, 28th

RENAL ASSOCIATION
4.30 P.M. (41, Portland Place, W.1.) Mr. I. H. Griffiths: Renal Arteriography. Dr. Robert Gaunt: Studies on Experimental "Eclampsia-like" Syndrome.

Thursday, 29th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. I. P. Todd: Elective Surgery in Management of Diverticulitis of Colon. (Hunterian lecture.)

UNIVERSITY OF LONDON
5 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. E. L. French (Melbourne): Epidemiological Aspects of Murray Valley Encephalitis.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Prof. J. K. Robertson, F.R.S.C.: An Experiment in Medical Education.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Prof. F. C. Ormerod: Aspects of Sinusitis.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
5.30 P.M. Dr. Pincus: Steroids in Ageing.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.30 P.M. (11, Chandos Street, W.1.) That Quackery Plays a Useful Part in Medicine Today. For: Dr. M. Marcus, Dr. S. H. Chazen. Against: Dr. D. Preiskel, Mr. I. Preiskel.

MANCHESTER MEDICAL SOCIETY
4 P.M. Prof. Bruce T. Mayes (Sydney): Could Eclampsia Disappear?

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Mr. W. M. Dennison: Advances in Surgery of Infancy and Childhood.

Friday, 30th

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Section of Epidemiology and Preventive Medicine.* Dr. John Gordon (Harvard): Epidemiologic Method in Modern Perspective.
8 P.M. *Section of Radiology.* Dr. E. W. Emery: Three Years' Use of a Cobalt Unit. Dr. D. Verel: Radioactive Phosphorus in Treatment of Polycythæmia Rubra Vera. Dr. F. E. Neal: Radioactive Phosphorus in Treatment of Fungoides.

FACULTY OF RADIOLOGISTS
4 P.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Prof. D. W. Smithers: Rotation Therapy.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
2 P.M. Prof. A. G. R. Lowdon: Surgical Management of Intestinal Obstruction.
4 P.M. Dr. J. E. Caughey (New Zealand): Hypopituitarism.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Mr. W. D. Doey: Indications for Tonsillectomy.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. Neville Mascall: *Trichomonas vaginalis.* (Presidential address.)

Births, Marriages, and Deaths

BIRTHS

CHALMERS.—On April 16, at St. David's Hospital, Cardiff, to Doreen, wife of Dr. T. M. Chalmers—a son.

GIBSON.—On April 11, at The Shiel, Elgin Road, Weybridge, to Graeme (Galbraith), wife of Dr. Eric Gibson—a son.

HELSBY.—On April 12, at Liverpool Maternity Hospital, to Joyce, wife of Raymond Helsby, F.R.C.S.—a daughter.

MARRIAN.—On April 14, to Biddy Kingsley Pillers, M.B., wife of Denis H. Marrian, PH.D.—a son.

THOMAS.—On April 13, at Plas Bowman, Caernarvon, to Nansi Wyn (née Owen), wife of Dr. R. Garym Thomas—a daughter (Amanda Claire).